Cost effectiveness analysis of olanzapine and risperidone

Most frequently prescribed antipsychotics for schizophrenia in Norway

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FOREWORD

Schizophrenia is a serious mental condition which interferes a normal life of a patient with schizophrenia diagnosis and imposes a substantial burden on caregivers. Schizophrenia is not fatal itself as a disease but it is involved with high risk of suicide, various types of adverse events caused by treatment medications, high costs of treatments including inpatient care and rehabilitation wards and substantial indirect costs. Therefore, if a novel antipsychotic medication is able to reduce significantly the schizophrenia symptoms without adverse events, the medication can alleviate social burden in a society as well as severe pain to the patients and the caregivers. There are tens of antipsychotic medications for schizophrenia being sold in Norway. This study is aimed at finding an optimal choice in terms of cost-effectiveness among the most popular antipsychotics for schizophrenia, olanzapine and risperidone.

All that glitters is not gold. I believe that discerning the gold is a duty of a health economist and this master thesis work was one part of stepping stones leading me to become the health economist. I would like to thank my supervisor, Eline Aas who has been supporting me with her knowledge, passion and warm heart since I began this master thesis in May in 2008. Thanks for Ivar Sønbø Kristiansen with constructive advices on my thesis. Lastly, thanks for infinite supports of my parents, family and friends in Korea.

My supervisor was Eline Aas, PhD., at the Institute of Health Management and Health Economics, University of Oslo.

Kun Kim
April in 2009 in Oslo.

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ABBREVIATIONS AND ACRONYMS

AIMS	Abnormal Involuntary Movements Scale
APA	American Psychiatric Association
CBA	Cost-Benefit Analysis
CBC	Community Based Care
CEA	Cost-Effectiveness Analysis
CGI Scale	Clinical Global Impression Scale
CPI	Customer Price Index
CUA	Cost-Utility Analysis
DALYs	Disability Adjusted Life-Years
DRG code	Diagnosis-Related Group code
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
EPSs	Extrapyramidal Symptoms
ESRS	Extrapyramidal Symptom Rating Scale
GAF Scale	Global Assessment of Functioning Scale
HAI	Hillside Akathisia scale
HTA	Health Technology Assessment
ICD-10	The International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICE	Incremental Cost Effectiveness
ICER	Incremental Cost Effectiveness Ratio
NMB	Net Monetary Benefit
PANSS	Positive and Negative Symptom Scale
PSA	Probability sensitivity analysis
QALYs	quality-adjusted life-years
QOL	Quality of Life
RCTs	Randomized Clinical Trials
SF-36	36-Item Short-Form Health Survey
SPS	Social Performance Schedule
TP	Willingness To Pay
YBOCS	Yale-Brown Obsessive Compulsive Scale

ABSTRACT

Background: Schizophrenia is a major public health problem throughout the world and known to be a major cause of disability. Antipsychotic medications are the mainstay of treatment for schizophrenia and olanzapine and risperidone are popular choices among atypical antipsychotics in Norway. Despite of the high number of prescribing olanzapine, however, cost-effectiveness of olanzapine versus risperidone is still debated.

Methods: A decision analytic model combined of a decision tree model and a Markov model was developed to compare the ICER of olanzapine and risperidone and determine the optimal alternative for schizophrenia treatment in Norway. The PANSS was used to measure effectiveness of the antipsychotics and costs were measured with a perspective of providers / funders of health and social care services in five years time frame. The Cochrane meta-analysis (1) and Norwegian cost analysis (2) provided the main source to operate the model.

Results: The total five-year expected cost per schizophrenic patient for olanzapine was NOK 1,878,072 and for risperidone NOK 1,943,868. The total expected PANSS reductions were 112.60 and 111.55 for olanzapine and risperidone, respectively, thus olanzapine was a dominant alternative to risperidone. However, the results from the PSA using Monte Carlo simulation indicated that olanzapine and risperidone are not different in terms of cost-effectiveness within 95% confidence interval. The ICE scatterplot demonstrated that the chance of olanzapine being an optimal alternative was 67.1% in the model.

Discussion and conclusion: Considering all of the uncertainties surrounding the costs and effectiveness of the olanzapine and risperidone, the model could not conclude that olanzapine was more cost-effective than risperidone in Norway. For more precise results, further clinical trials are recommended to follow up patients who drop out of the study and evaluate relapse rates categorized into compliant and noncompliant patients distinctively. However, the model seemed capable to figure the overall total costs per schizophrenic patient treated with antipsychotic medications in Norway. In addition, the model can be used to provide a basic frame of modelling patients with schizophrenia diagnosis and to facilitate further schizophrenia studies.

Chapter 1

INTRODUCTION

Schizophrenia is a serious mental disorder characterized by loss of contact with reality, hallucinations, delusions, abnormal thinking, and disrupted work and social functioning. This condition is a major public health problem throughout the world and known to be a major cause of disability. According to the study of 14 countries in 1999, active psychosis was ranked the third most disabling condition, after quadriplegia and dementia and before paraplegia and blindness (3). In spite of relatively low incidence rate, 0.1 to 0.4 per 1,000 population (4), schizophrenia has been one of the major contributors to the global burden of disease (5). In western countries, 1% of average gross domestic product was spent on the treatment, care and supports to people with schizophrenia diagnosis (6). In Norway, the direct and indirect costs associated with schizophrenic patients were calculated as NOK[1] 4 billion per year in 1995 and about NOK 7 billion per year were recalculated by reflecting inflation rates in 2002 i.e. schizophrenia was more costly than heart disease, cancer and rheumatic disease (7).

Pharmacological therapy has been a main treatment for schizophrenic patients and olanzapine and risperidone are the most popular antipsychotics for non-refractory schizophrenia (8). In Norway, according to Norwegian prescription database in 2007 (9), olanzapine and risperidone accounted about 55% of the total medication users for schizophrenia. As the most frequently prescribed antipsychotics for schizophrenia in Norway, there is an urgent need to critically examine olanzapine and risperidone based on evidence. This study was aimed at evaluating the incremental cost-effectiveness ratio of olanzapine versus risperidone in Norway by using a decision analytic model. The results will be of interest for those who are associated with schizophrenia; schizophrenic patients and their families, clinical practitioners and politicians in Norway.

This study consists of six chapters. The second chapter explores general knowledge about schizophrenia and schizophrenia treatments and the third chapter proposes a current issue and

[1] NOK refers to *Norwegian krone.*

objectives of this paper. In the fourth chapter, a decision analytic model and components of the model are described. In the fifth chapter, results produced by the model are presented. The results contain findings from a both discrete and stochastic model in order to demonstrate the consequences of including uncertainty into the estimations. Finally, the sixth chapter is to focus on weakness of the decision analytic model and deliberate feasibility of the findings being generalized into schizophrenia treatments in Norway.

Chapter 2

BACKGROUND

The term schizophrenia from the Greek roots *schizein* (to split) and *phren-* (mind) was coined by a Swiss psychiatrist, Eugen Bleuler in 1908. Schizophrenia is a severe and disabling mental illness and the symptoms and severity can vary over individual with schizophrenia.

2.1. Symptoms[2]

The symptoms of schizophrenia fall into three groups; *delusions and hallucinations*, *thought disorder and bizarre behavior* and *deficit or negative symptoms*. Recently, however, dichotomy classification is also used; positive and negative symptoms. A person may have symptoms from one or all.

Delusions are false beliefs that usually involve a misinterpretation of perceptions or experiences. For example, people with schizophrenia may experience persecutory delusions, believing that they are being tormented, followed, tricked, or spied on. They may have delusions of reference, believing that passages from books, newspapers, or song lyrics are directed specifically at them. They may have delusions of thought with drawl or thought insertion, believing that others can read their mind, that their thoughts are being transmitted to others, or that thoughts and impulses are being imposed on them by outside forces. Hallucinations of sounds, sight, smell, tastes, or touch may occur but auditory hallucinations and ideas of reference are the most frequently observed symptoms, found in about 70% of the patients (11). A person may *hear* voices commenting on his behavior, conversing with one another, or making critical and abusive comments.

Thought disorder refers to disorganized thinking, which becomes apparent when speech is rambling, shifts from one topic to another and loses its goal-directed quality. Speech may be mildly disorganized or completely incoherent and incomprehensible. Bizarre behavior may take the form of childlike silliness, agitation, or inappropriate appearance, hygiene or conduct.

[2] 2.1 Symptoms mainly referred to the Merck manual of medical information (10).

Catatonic motor behavior is an extreme form of bizarre behavior in which a person may maintenance a rigid posture and resist efforts to be moved or, in contrast, display purposeless and unstimulated motor activity. However, the tendency to bizarre thinking and peculiar sensory experiences is spread across the population more widely than is usually acknowledged by clinicians (12). Therefore, symptom assessment may be a threshold issue and should always be seen within the context of the person's overall emotional state and social functioning (13).

Deficit or negative symptoms of schizophrenia include blunted affect, poverty of speech, anhedonia, and asociality. Blunted affect refers to a flattening of emotions. The person's face may appear immobile; he makes poor eye contact and lacks emotional expressiveness. Events that would normally make a person laugh or cry produce no response. Poverty of speech refers to a diminishment of thoughts reflected in a decreased amount of speech. Answers to questions may be terse, one or two words, creating the impression of an inner emptiness. Anhedonia refers to a diminished capacity to experience pleasure; the person may take little interest in previous activities and spend more time in purposeless ones. Asociality refers to a lack of interest in relationships with other people. These negative symptoms are often associated with a general loss of motivation, sense of purpose, and goals.

In the past 20 years, the distinction between the two broad categories of *positive* and *negative* symptoms gained widespread popularity have often been employed in economic evaluations (14). While positive symptoms refer symptoms of schizophrenia such as delusions, hallucination, thought disorder and bizarre behavior, negative symptoms refer symptoms of schizophrenia such as poverty of speech, lack of motivation, apathy and inability to express emotions.

2.2. Diagnosis and prognosis

In the absence of a biological marker, diagnosis of schizophrenia relies on examination of mental state, usually through a clinical interview, and observation of the patient's behavior (13). As a standards used to diagnose schizophrenia, the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) is a global diagnostic tool (Appendix I). Diagnostic and Statistical Manual of Mental Disorders, 4^{th} Edition (DSM-IV) is also a diagnostic manual published by the American Psychiatric Association (Appendix II).

Both tools are used for clinical practitioners in Norway. Although ICD-10 states seven sub-types of schizophrenia, careful standardized diagnostic assessment, while useful for research, may not be necessary in clinical practice and the diagnosis of schizophrenia does not carry enough information for treatment planning (13).

Once a patient is diagnosed with schizophrenia, the patient may step forward following prognosis. In a longitudinal study, about one third of people with schizophrenia made a full recovery, about another one third showed improvement but not a full recovery, and a third remained ill in United States (15). In a recent community study, 62% showed overall improvement on a composite measure of symptomatic, clinical and functional outcomes at five years follow-up (16). Under specific factors patients with schizophrenia have bad prognosis. For example, the patients who gradually develop schizophrenia and live in the industrialized countries have bad prognosis. Substance abuse and a tendency to have social isolation are also the factors to cause bad prognosis (4).

However, different dimensions of outcome such as social functioning, clinical symptoms and cognitive performance are often only weakly related, showing heterogeneity within individuals and leaving room for improvement in one area even though problems may persist in others (17). In addition, findings are not always comparable across studies because an exact definition of what constitutes recovery has not been widely accepted (18).

2.3. Epidemiology and risk factors

Lifetime risk of schizophrenia is about 1% (19) and the relatively similar results are found in different cultures (4). The incidence of schizophrenia is relatively low. In a WHO study, almost all of ten countries showed incidence rates per year for adult patients with schizophrenia within a quite narrow range of 0.1 and 0.4 per 1,000 populations (4). In Norway, the annual incidence is 0.07 to 0.15 per 1,000 and the prevalence of schizophrenia is about 3 to 5 per 1,000. Schizophrenia occurs equally in males and females although typically appears earlier with the peak ages of onset being 20 to 28 years for males and 26 to 32 years for females (20). Much rarer are examples of childhood onset (21) and late (middle age) or very late onset (old age) schizophrenia (22). Although schizophrenia is not in itself a fatal disease, death rates of people

with schizophrenia are at least twice as high as those in the general population (13). Suicide, particularly, has emerged as a growing matter of concern, since lifetime risk of suicide in schizophrenic disorders has been estimated at above 10%, which is about 12 times that of the general population (23).

Risk factors for schizophrenia can, according to Cooper in 1978 (24), be grouped in three categories; *sociodemographic characteristics*, *predisposing factors* and *precipitating factors*. Within the Sociodemographic factor, the association between lower social class and schizophrenia in urban areas of developed countries is one of the most robust epidemiological findings (13). This is currently explained mainly by the *selection-drift hypothesis,* according to which individuals vulnerable to schizophrenia or with insidious onset of the disorder are either prevented from attaining higher class status or move progressively downward (25). However, it is possible that factors related to environmental conditions in lower class neighborhoods, such as occupational hazards, poor maternal and obstetric care or high psychosocial stressors, can play a role in some subgroups of people with schizophrenia. The complex social class related factors vary in occurrence of schizophrenia in different countries (13). In Norway, children of immigrates have high risk with schizophrenia and people living in urbane area have higher risk with schizophrenia than those living in inland (26).

Among the predisposing factors, genetic ones are most important (13). Genetic contribution to liability for schizophrenia has been well estimated around 60% (27), although models of genetic transmission, predisposing genes and the link between genetic actors and the phenomenology of schizophrenia are far from being identified. Available data leave considerable room for environmental influences, as shown by concordance rates of less than 50% in monozygotic twins and lifetime risk of about 45% in children of two schizophrenic parents. Given the heterogeneous nature of schizophrenic disorders, it is also possible that both genetic and non-genetic forms of the disorder exist (13).

In the variety of interpersonal, social and cultural variables postulated as precipitating factors, family environment remains the best documented (13). A large body of research shows that family interaction patterns characterized by unclear or fragmented communication, negative

affective style, criticism, hostility and over involvement are strong predictors of relapse in schizophrenia, although evidence of their influence on onset is quite limited (28). There are also indications that other less defined aspects of family environment may exert protective effects on vulnerable individuals (29).

2.4. Outcome measurements

The Positive and Negative Syndrome Scale (PANSS) is a medical scale used for measuring symptom severity of patients with schizophrenia. The scale has 30 items, each of which can be defined on a seven-point scoring system varying from 1 - absent to 7 – extreme. So a lower score indicates less severity. The scale can be divided into three sub-scales for measuring the severity of general psychopathology, positive symptoms, PANSS-P, and negative symptoms, PANSS-N (30). Since the PANSS is a convenient method to perceive improvement on a patient's mental status by treating with antipsychotics (30), it has widely used in the study of antipsychotic therapy.

The Global Assessment of Functioning (GAF) Scale is a numeric scale (0 through 100) used by mental health clinicians and physicians to subjectively rate the social, occupational and psychological functioning of adults. The GAF Scale has a number of ranked sentences descriptive of psychiatric disturbance, associated with numerical ratings and it is used as a quick and simple measure of overall psychological disturbance (31).

The Clinical Global Impression (CGI) Scale is a valid, reliable instrument to evaluate severity and treatment response in schizophrenia by thorough comparing with the PANSS and the GAF Scale (32). The CGI Scale is used to measure of symptom severity, treatment response and the efficacy of treatments on patients with mental disorders (33). Clinical trials with schizophrenia patients use the scale to assess both severity of illness and clinical improvement by comparing the conditions of the person standardized against other people with the same diagnosis (1). A seven-point scoring system is usually used with low scores showing decreased severity and/or overall improvement.

2.5. Treatment

The goal of treatment is to reduce severity of symptoms, prevent recurrences of symptomatic episodes and deterioration associated in functioning, and provide supports to allow functioning at the highest level possible (34). The pharmacological therapy has become a main treatment for schizophrenia since treatment was revolutionized in the mid 1950s with development of antipsychotic medications (35). Recently, the psycho educational therapy such as family therapy and cognitive therapy appeared as alternatives (36). However, those new alternative treatments are not practiced as standard treatments in Norway due to lack of sufficient documented studies over patients with schizophrenia (37).

The pharmacological therapy centred on the use of dopamine receptor blockers, such as chlorpromazine and haloperidol. Those antipsychotic medications are known as *typical antipsychotics*[3]. These agents had been shown to be more effective than placebo in controlling the positive symptoms of schizophrenia (38) and in moderating acute episodes of schizophrenia in clinical trials (39). However, although representing a major stepped forward in the treatment of schizophrenia when initially introduced, the overall impact of typical antipsychotic medications was disappointing (40). About 30% of individuals complying with typical antipsychotics regimens derived little or non benefit in terms of symptom control or reduction, while another 30% gained only partial relief (41).

In addition, typical antipsychotics appeared to involve high risk of side-effects (42). Chlorpromazine seemed to cause sedation, acute movement disorders, parkinsonism, hypotension and weight gain (38) and dystonia, akathisia and parkinsonism were found in patients with haloperidol (39). Besides, extrapyramidal symptoms (EPSs) were the most troublesome (40). EPSs refer to movement disorders that occur when there is a disruption of the brain's extrapyramidal system[4]. As a term, EPSs include following symptoms; akinesia (inability to initiate movement), akathisia (inability to remain motionless), dystonia (muscular spasms of neck - torticollis, eyes - oculogyric crisis, tongue, or jaw; more frequent in children)

[3] The term *typical* antipsychotics has following synonyms; conventional antipsychotics, first generation antipsychotics, classical neuroleptics and major tranquilizers.
[4] In human anatomy, the extrapyramidal system is a neural network located in the brain that is a part of the motor system involved in the coordination of movement

and tardive dyskinesia (involuntary, irregular muscle movements, usually in the face). Long-term use of typical antipsychotics drugs was associated with a high risk of debilitating neurological side-effects, notably tardive dyskinesia, as well as shorter-term effects such as akathisia and dystonia (40).

In response to the problems, the pharmaceutical industry had developed *atypical antipsychotics*[5]. Atypical antipsychotics are now widely used in the treatment of schizophrenia and, with the introduction of additional atypical agents. The negative symptoms responded better to atypical antipsychotics (21) and in general side-effects appeared less severely to atypical antipsychotics than conventional (40). As a results, recent guidelines in treating schizophrenia recommend the use of atypical antipsychotic medications (43,44).

2.6. Olanzapine and risperidone

Up to recently, the antipsychotic medications are the mainstay of treatment for schizophrenia and there is a trend towards greater use of new antipsychotics, especially olanzapine and risperidone (1). Because of their greater clinical efficacy and relatively benign adverse effects, olanzapine and risperidone became the most frequently prescribed antipsychotics (8). In UK, olanzapine and risperidone accounted for nearly half of all the antipsychotics prescribed and more than 90% of the atypical antipsychotics prescribed (45). The increase of using the antipsychotics is likely to be mirrored in low and middle income countries, where approximately 80% of people suffering from schizophrenia reside (46).

In United States, only clozapine, risperidone, olanzapine, and quetiapine carried FDA-approved labeling for use in the treatment of schizophrenia in 2002. At usual dosages, olanzapine and risperidone appeared with greater efficacy and a lower rate of adverse events than conventional antipsychotics (47-51). Although quetiapine was found to be superior to placebo, it did not provide any clinical advantage over conventional agents, such as chlorpromazine and haloperidol (52-54). Clozapine was also not considered a first-line agent for treating schizophrenia because of its propensity to cause agranulocytosis (55). Although olanzapine and

[5] The term *atypical* antipsychotics is a synonym of second generation antipsychotics and inconventional antipsychotics.

risperidone were approximately 10 times more expensive than conventional antipsychotics, researchers suggested that if they would reduce a person's need for inpatient services, their use could have resulted in an overall net reduction in costs (56,57).

Chapter 3

RESEACH QUESTION

As seen in chapter 2, olanzapine and risperidone became so-called novel antipsychotic medication. However, although the whole sale price of olanzapine is double as that of risperidone (58), the number of users with olanzapine is almost double to risperidone, as there are total 15,637 olanzapine users and 7,891 risperidone users in Norway in 2007 (9). A number of economic evaluations have been performed to compare olanzapine and risperidone. Nevertheless, the answer is still debated.

3.1. Literature review

Following electronic database were used to search economic evaluations of olanzapine and/or risperidone; Pubmed, Medline, Embase, Cochrane Library, PsychInfo and Google Scholar.

Olanzapine and risperidone are known as both safe and effective for the management of non-refractory patients but degree of efficacy on negative symptoms and aspects of side-effects appeared differently (51). In clinical trials, risperidone seemed associated with a greater frequency of orthostasis, corrected QT-interval prolongation, sexual dysfunction, and hyperprolactinemia (59,60). In an economic evaluation of antipsychotics for schizophrenia, risperidone caused EPSs significantly less frequently than with conventional agents but probably more frequently than other atypical antipsychotics at higher dosages (61). Also, more tardive dyskinesia cases were reported in taking risperidone than other atypical antipsychotics (62-65). In a study of adverse effects and costs, however, the author argued that because of its broad receptor-binding profile, olanzapine was linked to a higher frequency of anticholinergic effects than risperidone and weight gain occurred more often with olanzapine (59). In a clinical efficacy meta-analysis, it was argued that risperidone-treated patients had a lower risk of withdrawal and in terms of safety, risperidone-treated patients required less anti-EPS medication than patients treated with typical antipsychotic medications and lastly they concluded that risperidone might show clearer benefits in terms of efficacy than olanzapine (66).

Inconsistency of findings reported by various forms of comparing olanzapine and risperidone was found through literature review. A broad systematic review of atypical antipsychotic medications concluded that the evidence for the effectiveness of the new atypical antipsychotic medications was, in general, of poor quality, based on short-term trials and difficult to generalise to the whole population with schizophrenia (40). In addition, the tendency to favor antipsychotics for sponsorship pharmaceuticals had worsened the situation. According to the overview of clinical trials of olanzapine and risperidone, 33 of the 42 reports were sponsored by a pharmaceutical company and 90% of the studies reported that overall outcomes were in favor of the sponsor's drug (67).

3.2. Economic evaluation

An economic evaluation is the comparative analysis of alternative courses of action in terms of both their costs and consequences (68). The basic tasks of the economic evaluation consist of identifying, measuring and valuing costs and consequences the alternatives being considered in an incremental analysis, i.e. that the difference costs is compared with the difference in consequences (68). As a result, an economic evaluation enables patients and clinical practitioners to choose an optimal alternative, programme administrators to optimize resources allocation and policy makers to make informed decisions and to maximize utility to a society.

3.2.1. CEA, CUA and CBA[6]

A full economic evaluation often has three approaches; Cost-Effectiveness Analysis (CEA), Cost-Utility Analysis (CUA) and Cost-Benefit Analysis (CBA). First, in CEA, the incremental cost of a programme from a particular viewpoint is compared to the incremental health effects of the programme, where the health effects are measured in natural units related to the objectives of the programme. CEA are of use in situations where a decision maker, operating with a given budget is considering a limited rage of options within a given field. Second, in CUA, the incremental cost of a programme from a particular viewpoint is compared to the incremental health improvement attributable to the programme, where the health improvement is measured in quality-adjusted life-year (QALYs) gained or disability adjusted life-years (DALYs) gained. In contrast to CEA, CUA outcomes are generic as opposed to programme specific and

[6] 3.2.1 CEA, CUA and CBA mainly referred to Methods for the economic evaluation of health care (68).

incorporate the notion of value. Last, CBA requires programme consequences to be valued in monetary units, thus enabling the analyst to make a direct comparison of the programme's incremental cost with its incremental consequences in commensurate units of measurement. Because CBA converts all costs and benefits to money it is not restricted to comparing programmes within health care but can be used to inform resource allocation decisions both within and between sectors of the economy. Due to limit of available data, however, CEA with a decision analytic model was conducted.

3.2.2. Decision making in CEA

An optimal alternative is determined primarily upon results of comparing the incremental cost and the incremental effectiveness of alternatives. If an intervention is both less costly and more effective than a comparator, the intervention is *dominant* to or *dominating* the comparator. In

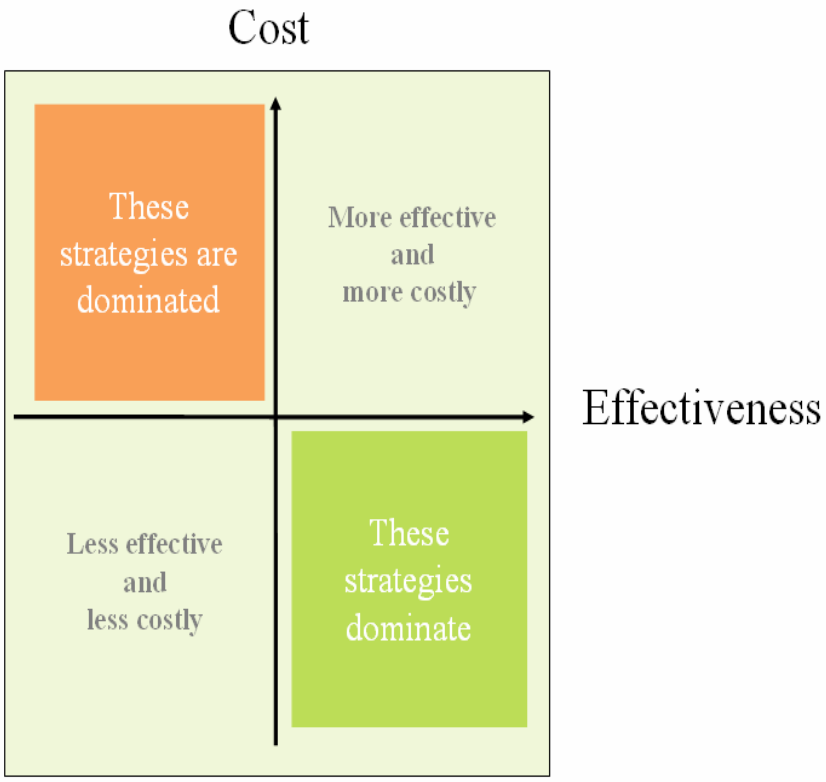


Figure 1. Dominant and dominated alternative in a cost-effect plane Adapted from Black (1990)

opposite, if an intervention both costs more and is less effective than a comparator, the intervention is *dominated* to the comparator. When effectiveness is plotted on the X axis, an option is dominated if it lies above and to the left of another alternative. The option below and to the right is referred to as dominant, or dominating (Figure 1).

If an intervention both costs more and is more effective or an intervention both costs less and is less effective than a comparator, external standards are needed. As one of the external standards is the incremental cost-effectiveness ratio (ICER), defined as

$$ICER = \frac{C_1 - C_0}{E_1 - E_0} = \frac{\Delta C}{\Delta E} \qquad [1]$$

ICER is defined as the ratio of the difference between costs of an intervention (C_1) and initial costs (C_0) to the difference between effects of the intervention (E_1) and initial effects (E_0). Using ICER, an optimal alternative is defined where the ICER is less than a threshold ratio or the minimum ICER among the ICERs of alternatives.

Although the ICER remains the most popular method of presenting the result of CEA, it does have draw backs. For example, the ratio gives no idea of the size or scale of the treatments or programmes being considered (68). So *Net benefit* was proposed as an alternative summary measure of the value for money of health care programmes (69). The net benefit approach employs a simple rearrangement of the cost effectiveness decision rule which is that an intervention is deemed cost effective if ICER is less than a threshold ratio. The *net monetary benefit* (NMB) is defined as

$$NMB = R_T \times \Delta E - \Delta C > 0 \qquad [2]$$

Where ΔE is the increase in effectiveness, R_T is the amount the decision maker is willing to pay per unit of increased effectiveness and ΔC is the change in costs. Willingness-to- pay (WTP) is the maximum monetary amount that an individual would pay to obtain a good. Consequently, $R_T * \Delta E$ has to be greater than ΔC for NMB to be positive.

3.2.3. Sensitivity analysis

In situations where no good clinical evidence exists, the cost-effectiveness analyst may proceed by making assumptions about the clinical evidence and undertaking sensitivity analysis of the economic results to different assumptions (68). In situations where heterogeneity in study population characteristics might have impacts on varying effects or costs, sensitivity analysis is also preferable.

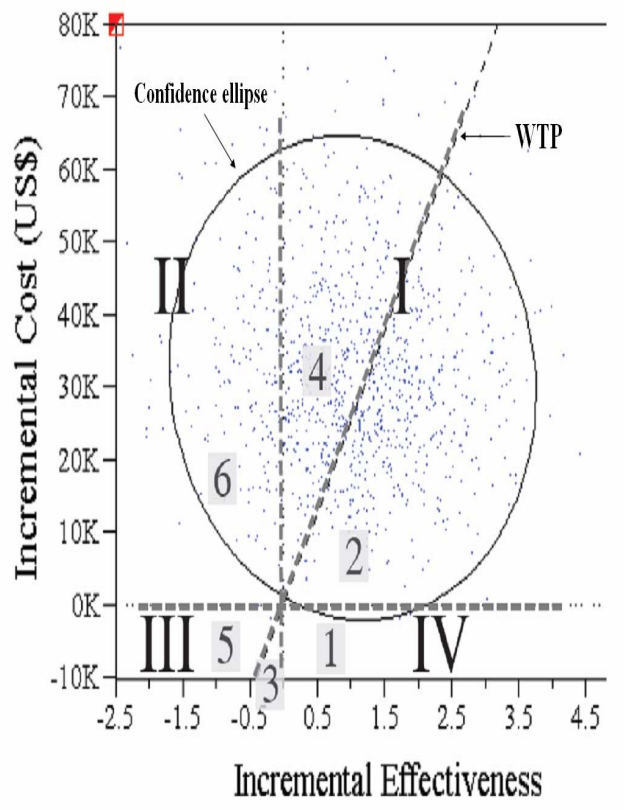
To investigate the robustness of a study with a form of mathematical modelling, when the study contains potential to wave the results by parameters associated with uncertainty, one-way sensitivity analysis can demonstrate changes of results by varying an uncertain parameter within a range of variables. Multiple-way sensitivity analysis examines simultaneous changes of results by varying more than two uncertain parameters. A tornado diagram is a set of one-way sensitivity analyses brings together in a single graph. Each expected value generated by varying uncertainty related parameters is displayed on a horizontal axis in rank order by size, so the parameter with the largest potential impact on results can be seen in the diagram.

However, those sensitivity analyses, called *deterministic sensitivity analysis*[7] have following drawbacks especially in using decision analytic modelling. Drummond (68) argued that first, with standards (deterministic) sensitivity analysis it is only practical to vary a small number of parameters simultaneously but most models include more input parameters than limits one or two. Second, when input parameters in the model are correlated, the correlation is not handled. Third, there is no suitable summary measure of the implications of the uncertainty. In face of the limitations of standard sensitivity analyses, *probabilistic sensitivity analysis* (PSA) has been discussed (70). In PSA, input parameters are defined in as probability distributions to reflect the parameters' full uncertainty. By using *Monte Carlo simulation* propagating input parameters within randomly sampled from the probability distributions, the end result is computed as a large number (for example, 10,000) of sets of expected costs and effects that combined parameter uncertainty in the model. An advantage of the PSA using Monte Carlo simulation is that uncertainty associated with all of the parameters can be incorporated in an analysis. Sampling parameter values from probability distributions (rather than from a deterministic range,

[7] Deterministic sensitivity analysis is named after that the set of range with parameters is deterministic.

upper and lower bounds) places greater weight on likely combinations of parameter values, and simulation results quantify the total impact of uncertainty on the model within confidence level, which can be placed in the analysis results.

As one of outputs of the PSA using Monte Carlo Simulation, the Incremental Cost-Effectiveness (ICE) scatterplot is used for decision making. The ICE scatterplot uses a form of the standard Cost-Effect plane to plot points for each iteration in the simulation output. The ICE scatterplot includes a single set of points representing pairs of the incremental cost and effectiveness values from the simulation results, based on a comparator relative to a baseline alternative. The WTP line in the graph intersects points having the specified ICER value, and the region below the line includes cost-effective points. For each plotted result, the comparator will be cost-effective (relative to the baseline) if it falls within the three component regions, i.e. *Section 1 to 3* in Figure 2.



Section	Interpretation
1	Comparator *dominates* the baseline
2	Comparator is more costly and effective, and its ICER is less than or equal to the WTP, so it is *cost-effective*
3	Baseline is more costly and effective, but its ICER is greater than the WTP, so the comparator is *optimal*
4	Comparator is more costly and effective, but its ICER is greater than the WTP, so the baseline is optimal
5	Baseline is more costly and effective, and its ICER is less than or equal to the WTP, so it is optimal
6	Baseline dominates the comparator
Indiff	Indifference, incremental cost and effect close to zero

* Source: TreeAge Pro 2009 user's manual

Figure 2. The ICE scatterplot and interpretation

3.3. Research question

This study was aimed at comparing the ICER of olanzapine and risperidone and determining which alternative is a more cost-effective antipsychotic medication for schizophrenia in Norway. The perspective of the analysis was constrained to providers of health and social care services. While this did not extend to a full societal perspective, it did include those perspectives where the use of atypical antipsychotics is likely to have a major impact. To be consistent with the population targeted by current clinical guidelines (71), the analysis was restricted to a consideration of the likely costs and consequences for patients with schizophrenia in age range from 16 to 65 in Norway. On a base of clinical guidelines and prior decision analytic models, a decision analytic model was developed to compare the expected costs and consequences of schizophrenic patients with the antipsychotic medications and estimate the range of uncertainty surrounding the results. One-way sensitivity analysis, two-way sensitivity analysis and the PSA were performed to examine robustness of findings in association with uncertainty.

Table 1. Core issues in the economic evaluation

Core issues	
Comparators	Olanzapine 10mg and risperidone 4 mg
Objective	Comparing ICER of the antipsychotics
Population	Diagnosis: schizophrenia (DSM-IV), age 18-65 in Norway
Perspective	Providers/funders of health and social care services
Approach	CEA with a decision analytic model combined of decision tree model and Markov model
Time frame	Five years
Outcome measures	The PANSS score
Main source of the effectiveness	Meta-analysis (Cochrane 2005)
Unit costs	Medication market prices, clinician's fee schedules, empirical cost data in Norway
Cost currency	Norwegian Krone (NOK) in 2008
Discount rate (%)	4%
Sensitivity analysis	Probability sensitivity analysis, one–way and multiple-way sensitivity analysis

Chapter 4

METHODS

When extensive prospective health economic data are limited and/or based on varying assumptions, economic decision model are frequently used to identify cost effective solutions (72). This type of method is relatively rapid to estimate the economic impact of antipsychotic medications and provides the flexibility to compare different antipsychotics, to incorporate different treatment patterns, structures and duration (73). Although in clinical medicine and epidemiology the randomized, double-masked, prospective trial may be considered essential, social and economic analysts have long used modelling to simulate real-life usage. Also, models allow individual variables to be altered in a manner that is impossible in prospective trials (74).

4.1. A decision analytic model

The decision analytic model examined costs and health consequences of treatment alternatives; olanzapine 10mg and risperidone 4mg over five years in Norway. The model was based on Norwegian electronic physician guidebook (34), a review of pharmacoeconomic modeling on schizophrenia (72) and decision analytic models in prior studies (75-77).

Tree Age Pro Healthcare Module 2008 program was used to calculate ICER of the comparators and operate the PSA, one-way sensitivity analysis and two-way sensitivity analysis. In the model, both pathways of olanzapine and risperidone are equally given but probabilities for each of the pathways are different and that, along the difference in the resource use, have impact on results. There are four main node types: *A decision node* indicates a choice facing the decision maker. *A chance node* is an event which has multiple possible outcomes and is not under the decision maker's control. *A terminal node* denotes the endpoint of a scenario. *A Markov node* indicates the beginning spot of Markov process[8].

[8] A Markov process is a mathematical model for the random evolution of a memoryless system, that is, one for which the likelihood of a given future state, at any given moment, depends only on its present state and not on any past states.

4.2. Model description

The model consists of two distinct stages to reflect the treatment process for schizophrenia patients in Norway. First, the *acute stage* reflects the initial 16 weeks period of acute treatment in which the treatment is primarily aimed at reducing the current acute symptoms and stabilizing the patients. During the initial 16 weeks, a clinician evaluates responds of the initial treatment and the switched antipsychotics. Second, the *maintenance stage* (from the 16th week to 5th year) is a stage of prolonged longer term preventative treatment aimed at preventing acute relapses. Figure 3 illustrates a simplified structure of the model.

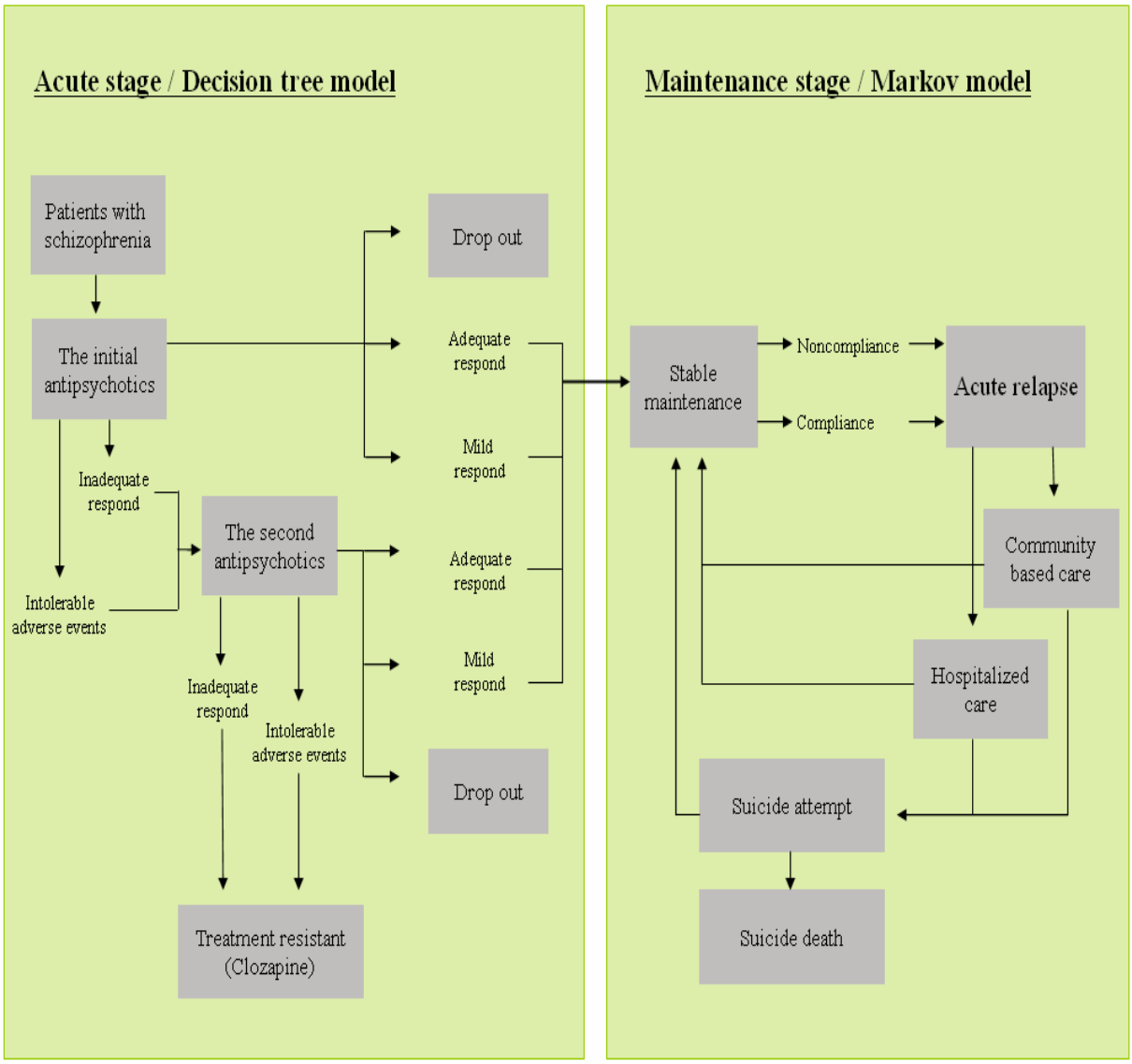


Figure 3. A simplified structure of the decision analytic model

4.2.1. The acute stage (from the baseline to 8th or 16th week)

At the beginning, a clinician makes a decision whether to treat patients with schizophrenia diagnosis with olanzapine 10mg or risperidone 4mg. Doses of the antipsychotics were based on both HTA guideline for cost-effectiveness analysis for antipsychotics[9] (40) and clinical trials providing the effectiveness data in the model (71,78). Some of the patients do not complete the treatments and leave study early due to, for example, adverse effects and lack of medication's efficacy (noted as drop out in the model). It is common in schizophrenia pathology that patients often drop out of health care systems and reappear at hospitals later (72). The others continue the treatment. In the 8th week, the clinician evaluates the patients' mental state and responds to the initial treatment. The patients who have more than 40% reduction from the baseline PANSS are classified as *adequate respond*. The patients who have between 20% and 40% reduction from the baseline PANSS score are classified as *mild respond*. The patients with adequate respond or mild respond continue the initial treatment and enter the maintenance stage unless the adverse events are intolerable. If the adverse events are intolerable or the reduction in the baseline PANSS score is less than 20% (*inadequate respond*), the clinician switches the initial (1st line) treatment to the second (2nd line) treatment, i.e. olanzapine to risperidone or visa versa. It was assumed that prior use of taking an antipsychotic did not influence the effectiveness of the use of the other antipsychotics. The switching strategy is to reflect clinicians' practice dealing with adverse events. When adverse events occur to schizophrenic patients, according to a Spanish non-interventional cross-sectional study (79), about half of the patients continued the treatment with no action, 30% of them used medication for handling the adverse events and only 5 % switched the initial antipsychotics (80).

Some of the patients drop out of the second treatment between the 8th and 16th week. At 16th week, the clinician evaluates the patients' mental state and the respond to the second treatment. Those who have either *adequate respond* or *mild respond* continue the second treatment and enter the maintenance stage unless the adverse events are intolerable. If the adverse events are intolerable or the responds to the second treatment is *inadequate*, the clinician switches to treatment with clozapine (3rd line).

[9] The recommended dose of antipsychotics for schizophrenia: olanzapine; 5–20 mg daily, risperidone; 3–6 mg daily, and clozapine; 150–450 mg daily (40).

4.2.2. The maintenance stage (from 16th week to 5th year)

The maintenance stage was developed in the form of Markov model firstly to describe acute relapse and stabilizing process and secondly to track the long term treatment experience of patients and the associated health care resource use and costs. The pattern of repeated acute relapses of symptoms is typically seen in the majority of patients with diagnosed schizophrenia (81) and the Markov model is suited to modelling repeated events or the progression of chronic diseases such as schizophrenia (72). In the maintenance stage, patients are assumed to remain on a stable condition with controlled symptoms unless they experience an acute relapse of symptoms in a three months cycle which repeats 20 times to complete five years time frame. According to methodology study in economics evaluation (82), an informative prediction model has five years time frame, preferably with the ability to project throughout a patient's lifetime.

In the maintenance stage, the patients are assumed to continue the initial or second treatment that they respond on adequately or mildly without intolerable adverse events during the acute stage. In practice, however, a certain percentage of the patients are always noncompliant, which influences the relapse rate (83). Acute relapse among noncompliant patients is more frequent, disruptive, and severe (84). In the beginning of the maintenance stage, acute relapse occurs at a lower rate for compliant patents than for noncompliant patients. Patients without acute relapse remain in the stable maintenance stage until the end of the cycles. Once an acute relapse occurs, the patients move into one of two modalities of health care service depending on the setting of their treatment; hospitalized care or community based care (CBC). During the acute relapse, some of the patients attempt suicide. Some of those with a suicide attempt survive and the rest ends in death. After completing their treatment, the patients return to the stable condition with controlled symptoms and go through this process in another cycle. In the maintenance stage, it is assumed that suicide is the only cause of death and the others remain in the repeating cycles.

In the decision analytic model, following assumptions were additionally made. In the maintain stage, it is assumed that the PANSS score decline with 5% every cycle in the first year in order to reflect that the symptoms relieve with time passing. In a long term clinical trial of olanzapine and risperidone, it was reported that the proportion of patients with either adequate respond or mild respond increased with 50% from the 8th until the 28th weeks (1). However, since the aim

of long term treatment is avoidance of relapse, not reducing the acute symptoms, PANSS score reduction was not considered from the second year in the model. Therefore, only the acute stage and the first year in the maintain stage produced accessible data for performing cost effectiveness analysis. The utility of the maintenance stage from the second to fifth year was limited as supplement to calculate the expected value of the costs in five years. Another additional assumption was that the compliance rate was applied only for the first year in the maintenance stage due to lack of available data.

Table 2. Definition of model elements

Model element	Definition
Acute stage	Initial treatment period targeted at reducing the acute symptoms of a schizophrenic episode
Drop out	Incomplete treatment and leaving study early
Adequate respond	Reduction from the baseline in PANSS > 40%
Mild respond	Reduction from the baseline in PANSS >20% and < 40%
Inadequate respond	Reduction from the baseline in PANSS < 20%
Intolerable adverse events	A condition that a patient has to stop taking the antipsychotic due to serious side effects
The initial treatment	1^{st} line treatment., an antipsychotic that a patient is initially prescribed for
The second treatment	2^{nd} line treatment, the other alternative that a patient is switched from 1^{st} line treatment due to intolerable adverse events or inadequate respond.
Maintenance stage	The prolonged treatment, after acute symptoms have been reduced, targeted at delaying or avoiding any repeat acute episodes
Non compliance	Refusal to adhere to a treatment regime which have adequate or mild symptom control
Acute relapse	A new episode of schizophrenic symptoms that require clinical management, experienced after a period of stabilizing
Hospitalized care	Acute care set in the context of inpatient care in a hospital
Community based care	Acute care set in the context of a community service
Suicide attempt	Suicide attempt during an acute relapse episode in the maintenance stage
Death	Death due to suicide attempt

Below is summary of assumptions in the model.

- The initial treatment does not influence on effectiveness of the second treatment.
- In the maintenance stage, patients continue the initial or second treatment which they have the adequate or mild respond without intolerable adverse events during their acute stage.
- In the maintenance, stage patients remain on a stable condition with controlled symptoms unless they experience an acute relapse of symptoms.
- One cycle has the 3 months time perspective.
- Suicide death is only way out of the cycle and the rest of them stay in the repeating cycle in the maintenance stage.
- 5% of PANSS score fall down to all of the patients in the 1^{st} to 4^{th} 3 months-cycle in the maintenance stage.
- The maintenance stage begins with acute relapse or non acute relapse from the 5^{th} cycle.

4.3. Clinical effectiveness and probabilities

Although it is primarily a clinical issue, the availability of good quality data on the effectiveness of the treatments being assessed is crucial to the CEA. In fact, CEAs are more often criticized for the quality of the effectiveness evidence on which they are based, rather than for the subsequent economics (68). To search quality data on the effectiveness of olanzapine and risperidone, I used following electronic databases; Pubmed, Medline, Embase, Cochrane Library, PsychInfo, Cinahl, Social Services Abstracts, Sociological Abstracts, Eric, International Bibliography of the Social Sciences, Social Sciences Citation Index, Social Care Online, C2-SPECTR, SveMed, BiblioMap, Bibsys and Google Scholar.

A meta-analysis in a systematic review; Risperidone versus olanzapine for schizophrenia (1) provided main effectiveness and probability data used in the model. The meta-analysis included 16 studies after the inclusion criteria reviewing 52 studies and excluded studies with inadequate level of allocation concealment. This was one of strengths of the meta-analysis as Drummond argued that probably the most important aspect is the random allocation of patients to treatment groups for methodological features of a well-designed study to assess effectiveness (68). Besides, another advantage of using the meta-analysis is of comprehensiveness in the effectiveness evidence. Through investigating a wide extent of citations of the studies, the systematic review could handle the issue that selective use of clinical data in an economic evaluation results in a more favourable cost effectiveness assessment than would have been the

case if all the available data are used (85). Appendix III summarizes studies used as source providing the effectiveness and probability data on olanzapine and risperidone in the model.

In the acute stage, the respond to the initial and second treatment referred to the short term (8weeks) effectiveness data. The decision analytic model did not refer to the long term (28weeks) effectiveness data but used them as the base of notion that 5% reduction in PANSS score takes a place in each cycle in the first year. To input actual reduced PANSS score as the effects of olanzapine and risperidone in stead of reduced percentage into the decision analytic model, the following procedure was needed. In the short term study of olanzapine and risperidone, the mean baseline PANSS score of the population was 80.9 (SD=13.0, the mean baseline PANSS score of the olanzapine group=81.2, that of the risperidone group=80.7) (71). The mean PANSS reduction from the base line of the adequate respond group was assumed 50% and those of the mild respond and inadequate group were 30% and 10%, respectively. Therefore, the mean PANSS reduced score of the adequate respond group was 40.5(=80.9*0.5), the mean PANSS reduced score of the mild respond group was 24.3(=80.9*0.3), the mean PANSS reduced score of the inadequate group was 8.1(=80.9*0.1) and lastly, the mean PANSS reduced score of 5% reduction was 4.5(=80.9*0.05).

Table 3. Clinical data on response and intolerable adverse events to the antipsychotics

	Olanzapine n / N (%)	Risperidone n / N (%)	Reference
Adequate respond, >40% reduction from the baseline in the PANSS/ 8weeks	50/277 (0.181)	62/275 (0.225)	(71), (78)
Mild respond, > 20%< 40% reduction from the baseline in the PANSS/ 8weeks	69/277 (0.249)	55/275 (0.200)	(71), (78)
Inadequate respond, < 20% reduction from the baseline in the PANSS/ 8weeks	158/277 (0.570)	158/275 (0.575)	(71), (78)
Adequate respond, >40% reduction from the baseline in the PANSS/ 28weeks	70/172 (0,407)	63/167 (0,377)	(51)
Mild respond, > 20%< 40% reduction from the baseline in the PANSS/ 28weeks	41/172 (0,238)	60/167 (0,359)	(51)
Inadequate respond, < 20% reduction from the baseline in the PANSS/ 28weeks	31/172 (0,355)	44/167 (0,263)	(51))

* Source: a systematic review; risperidone versus olanzapine for schizophrenia (1)

Most of the probabilities were based on the meta-analysis (1), but some probabilities referred to other studies. Following three, the probability of acute relapse to noncompliant patients, the

probability of acute relapse from the second year and the probability of hospitalized care referred to estimates or expert's opinions[10] from the prior economic evaluations using an analytic model (75-77).

Table 4. Probabilities used in the model

Probability	Olanzapine	Risperidone	Reference
Acute stage (8 or 16weeks)			
Drop out	0.189	0.221	(86), (71), (87), (78), (88), (89), (51)
Continue	#[1]	#	-
Adequate respond	0.181	0.225	(71), (78)
Mild respond	#	#	-
Inadequate respond	0.570	0.575	(71), (78)
Intolerable AE	0.095	0.097	(90)
Tolerable AE	#	#	-
Maintenance stage			
Noncompliance[2, 3]	0.141	0.115	(90), (91), (92), (51)
Compliance	#	#	-
Acute relapse, compliance	0.098	0.365	Estimated (Appendix IV)
Non acute relapse, compliance	#	#	-
Acute relapse, noncompliance	0.750	0.750	(77)
Non acute relapse, noncompliance	#	#	-
Acute relapse (from 2nd year)	0.094	0.094	(76)
Non acute relapse (from 2nd year)	#	#	-
Hospitalized care	0.700	0.700	(75)
Community based care	#	#	-
Suicide attempt	0.013	0.018	(93), (90), (71), (92), (51)
No suicide attempt	#	#	-
Suicide death	0.397	0.395	(71), (78), (89)
Suicide survival	#	#	-

* Main source: A systematic review; Risperidone versus olanzapine for schizophrenia (1)

1. The sharp note (#) indicates the probability which makes sum of branches one at the chance node. For example, the sum of the probability of drop out and continue has to be one so the probability of continue, olanzapine is 0.801(=1-0.189).
2. As a surrogate measure of noncompliance, leaving the study early due to adverse events was used.
3. Noncompliance and compliance rate were applied only until the 4th cycle.

[10] The expert team consisted of a published health economist in the mental health sector and three clinical psychiatrists/psychotherapists to provide clinical and health economic experience of treating schizophrenia in Germany (75).

The probabilities of acute relapse for complaint patients with olanzapine and risperidone were estimated on the base of relapse/hospitalization data (94) and an explanatory estimating process, illustrated in Appendix IV. All of the probabilities used in the model are summarized in Table 4.

4.4. Health care resources

Patients with schizophrenia are expected to consume different levels of health care resource during the treatment. Since the healthcare resource consumed in this study are constrained to the perspective of the providers in the health and social care services, the health care sectors and the other sectors in schizophrenia treatment were identified, measured and valued. Resources in the health care sector consist of factors such as drugs, equipment, hospitalization, physician visits and so on. Resources consumed in other sectors are likely to be, for example, use of homemaker services, nursing home care or voluntary services (68). The patient and family resources[11] and productivity losses were not included.

In this study, the amount of each service unit cost referred to the costs of services for schizophrenic patients in Norway (2). In 1999, Rund and Ruud estimated that the total direct costs of mental health services for schizophrenic patients were NOK 1,158 million per year (US$ 164 million). The estimation was based on gross expense for the institutions including all overhead costs[12] in duration of 4weeks in 1994. All treatment units serving 6 catchment areas with a total population of 425,000 (9.9% of the population of Norway) were considered to be representative of the country as a whole (2).

4.4.1. Drug cost

Drug costs referred to the price list of medication sold in Norway (58). In the model, patients continue to use olanzapine 10mg or risperidone 4mg daily (or clozapine 300 mg as 3rd line treatment). As one common type of medications to handle EPSs in Norway, Biperiden 2mg is taken twice a day for patients with EPSs in the model. The costs of taking Biperiden were

[11] The patient and family resources could consist of out of pocket expenses in traveling to hospital, various co-payments and expenditure in the home. The time could either be from leisure activities or work time, which would affect its valuation (68).
[12] All overhead costs were defined as shared costs for administration, technical services and other services in the Study (2)

related to the probabilities of EPSs occurring in the model. The probabilities of EPSs occurring seemed lower for long-term use than for short-term use.

Table 5. The probability of EPSs occurring

Period	olanzapine	risperidone	Reference
by 8 weeks	0.35	0.48	(51), (95)
by 3 to 12 month	0.19	0.33	(51), (95)
over 52 weeks	0.08	0.11	(90), (92)

* Source: a systematic review; risperidone versus olanzapine for schizophrenia (1)

4.4.2. Community based care cost

Since schizophrenia is a chronic condition and relapse is common, schizophrenic patients are expected to consume community based care (CBC) on a regular basis even if the symptoms are stabilized. Considering the nature of schizophrenia, CBC was divided in three ways in the model.

Table 6. Total costs for CBC in 3 months (NOK in 2008)

	Number of visit	Cost per visit	Proportion of use	NOK
CBC stable maintenance				
Psychiatrist + psychologist	6 visits + 1 GP	760	0.5	2,425
GP	6 visits	289	0.2	347
Out-patient	6 visits	1,800	0.3	3,240
Total			1.0	6,011
CBC non-hospital relapse management				
Psychiatrist + psychologist	18 visits	760	0.5	6,840
GP	18 visits	289	0.2	1,040
Out-patient	18 visits	1,800	0.3	9,720
Total			1.0	17,600
CBC post-hospital relapse management				
Psychiatrist + psychologist	18 visits	760	0.65	8,892
GP	18 visits	289	0.10	520
Out-patient	18 visits	1,800	0.25	8,100
Total			1.00	17,512

In the maintenance stage, patients consume CBC on a regular basis unless they experience acute relapses (*CBC stable maintenance*). Some of the patients with acute relapse increase CBC for the complete duration of their acute relapse (*CBC non-hospital relapse management*). Alternatively, rest of the patients with acute relapse move into a hospital and consume CBC for the remainder of their acute relapse after being discharged (*CBC post-hospital relapse management*). The cost per visit referred to fee schedules for GP, psychiatrist, psychologist and out patient clinic in Norway (97). The number of clinical services visit and the proportion of use referred to experts' opinion (75).

4.4.3. Residential care cost

In the model, the residential care consists of home, partial sheltered accommodation and full sheltered accommodation. Schizophrenic patients are expected to stay in one of those residential modalities depending on severity of the symptoms. The residential care cost occurs concurrently along with CBC services and the residential care cost does not count the days of hospitalization when patients with acute relapse are hospitalized. The partial sheltered accommodation cost per day referred to *day unit care cost* and the full sheltered accommodation cost per day referred to *psychiatric nursing home cost* from empirical cost data in Norway (2). The cost values were converted into 2008 by Customer Price Index (CPI)[13]. The proportion of use referred to experts' opinion (75).

Table 7. Total costs for residential care in 3 months (NOK in 2008)

	Cost per day	Cost for 3months	Proportion of use	
Home	0	0	0.8	0
Sheltered accommondation (partial)	67	6,020	0.1	602
Sheltered accommondation (full)	1,584	142,590	0.1	14,259
Total	-	-	1.0	14,861

[13] Web-based Inflation calculator: http://www.ssb.no/vis/kpi/kpiregn.html, authorized by Statistics Norway (Statistisk sentralbyrå)

4.4.4. Hospitalized care cost

During 8 weeks of the acute stage, the patients are hospitalized for 4 weeks. The length of hospitalization in the acute stage was based on a short-term clinical trial for schizophrenia (71). The 2nd line respondents are assumed to be hospitalized for another 4 weeks because the clinician needs another period of evaluation. The hospitalized care cost per day refers to the total cost of *acute wards, sub acute wards* and *long term wards* for schizophrenic patients in Norway (2) and the cost values reflected inflation rates into 2008.

Table 8. Total costs for hospitalized care in the acute stage (NOK in 2008)

	Cost per day[1, 2]	Hospitalized day(s)	Total
1st line respondent	2,611	28	73,101
2nd line respondent	2,611	56	146,202

In the maintenance stage, the 2nd line respondents with acute relapse were considered to have a longer stay in hospital than the 1st line respondents with acute relapse. The length of hospitalization for the 1st line and 2nd line respondents are 30 days and 60 days, respectively referred to expert opinion (75). The length of hospitalization for 3rd line (clozapine) patients is assumed to equal to the 2nd line respondents (60 days). In the maintenance stage, after leaving the hospital the patients receive the CBC post-hospital relapse management and the residential care for the reminding days in the 3 month cycle. Thus, the 1st line respondents spend 60 days in the residential care while the 2nd line respondents expend 30 days in residential care.

Table 9. Total costs for hospitalized care in 3 months in the maintenance stage (NOK in 2008)

	Hospitalized (days)	Hospitalized care cost[1]	Post-hospital CBC [2]	Post hospital residential care[3]	Total
1st line respondent	30	78,323	17,512	9,907	105,742
2nd line respondent	60	156,645	17,512	4,954	179,111

1. The cost per day of hospitalized care referred to NOK 2,611 (2).

2. Table 6

3. Table 7

4.4.5. Suicide-related cost

The first strategy was to find default costs of suicide attempt based on the Norwegian diagnosis-related group[14] (DRG) code; poisoning and toxic effects of drug. However, since no such code existed in Norwegian DRG, I referred the direct costs of suicide death and suicide attempts in U.S. Based on over 32,000 of completed suicides and 109,500 hospitalizations for suicide attempts in 1994, the direct cost of suicide attempt was US$ 1,860 and the direct cost of suicide death was US$ 575 (96). In 2008, they were NOK 15,891 and NOK 4,913, respectively with reflecting currency rate (US$ 1=NOK 7.1) and CPI inflation.

4.4.6. Drop out cost

Although some of the patients with schizophrenia drop out of clinical trials and the researcher fail to track them down, they are likely to continue other types of treatment. Thus, the health care resource consumed by the drop out patients was assumed the patients would suffer from uncontrolled symptoms and remain in hospitalized care all the following cycles. The drop out costs for the first year was multiplied with the daily inpatient cost, NOK 2,611 per day for 365 days. From the second and fifth year, the drop out costs was four times more than the first year cost. Since there was uncertainty in association with the drop out cost, one-way sensitivity analysis and the PSA were conducted to examine potential of the drop out cost to vary the results.

[14] Diagnosis-related group (DRG) is a system to classify hospital cases into one of pre-defined diagnosis groups. DRG is based on ICD 10 diagnoses, procedures, age, sex, discharge status, and the presence of complications or comorbidities.

Table 10. Cost per schizophrenic patient in Norway (NOK in 2008)

	NOK	Sources
Acute stage		
Drug Cost		
Olanzapine, 8weeks	1,707	(58)
Risperidone, 8weeks	849	(58)
Olanzapine switched from risperidone, 16weeks	2,556	(58)
Risperidone switched from olanzapine, 16weeks	2,556	(58)
Hospitalized care (HC) cost		
1st line respondent (28 days)	73,101	(2)
2nd line respondent (56 days)	146,202	(2)
Maintenance stage (3 months)		
Drug Cost		
Olanzapine 10mg	2,743	(58)
Risperidone 4mg	1,364	(58)
Clozapine 300mg	1,162	(58)
Biperiden 2mg, olanzapine user by 1st year	14	(58), (51), (95)
Biperiden 2mg, risperidone user by 1st year	25	(58), (51), (95)
Biperiden 2mg, olanzapine user from 2nd year	6	(58), (90), (92)
Biperiden 2mg, risperidone user from 2nd year	9	(58), (90), (92)
Community based care cost		
Clinical management, symptoms stable	6,011	(97)
Clinical management, acute relapse	17,600	(97)
Residential care	14,861	(2)
Hospitalized care cost		
1st line respondent (30 days)	105,742	(2)
2nd line respondent (60 days)	179,111	(2)
Suicide cost		
Suicide attempt	15,891	(96)
Suicide death	4,913	(96)
Drop out cost		(2)
The first year (365 days)	791,911	(2)
From the second the fifth year	3,167,645	(2)

Chapter 5

RESULTS

5.1. Costs and health consequences

In the first year, the total expected cost per schizophrenic patient with olanzapine was NOK 549,740 which was NOK 13,131 lower than risperidone (NOK 562,871). From the second to fifth year, the expected total cost per schizophrenic patient with olanzapine was NOK 1,328,332, which was NOK 52,665 lower than risperidone (NOK 1,380,997). The annual average cost per schizophrenic patient using both olanzapine and risperidone were about 39% deceased compared to the total expected cost in the first year. The total five-year expected cost per schizophrenic patient with olanzapine was NOK 1,878,072 which was NOK 65,796 lower than risperidone (NOK 1,943,868).

Table 11. The total expected costs (NOK in 2008)

	1 year	2-5 year	Annual average from 2nd year	Total
Olanzapine	549,740	1,328,332	332,083	1,878,072
Risperidone	562,871	1,380,997	345,249	1,943,868
Incremental cost	13,131	52,665	13,166	65,796

In the first year, the total expected PANSS reductions were 112.60 and 111.55 for olanzapine and risperidone, respectively. The expected incremental costs for risperidone were NOK 13,131 and the expected incremental effectiveness for risperidone was -1.05. Therefore, olanzapine was a dominant alternative to risperidone.

Table 12. Cost effectiveness analysis results in the first year (NOK in 2008)

Strategy	Cost	ΔC	Effectiveness	ΔE	C/E	ICER
Olanzapine	549,740	-	112.60 PANSS	-	4,882 NOK/PANSS	-
Risperidone	562,871	13,131	111.55 PANSS	-1.05 PANSS	5,046 NOK/PANSS	Dominated

* ICER refers to [Equation 1].

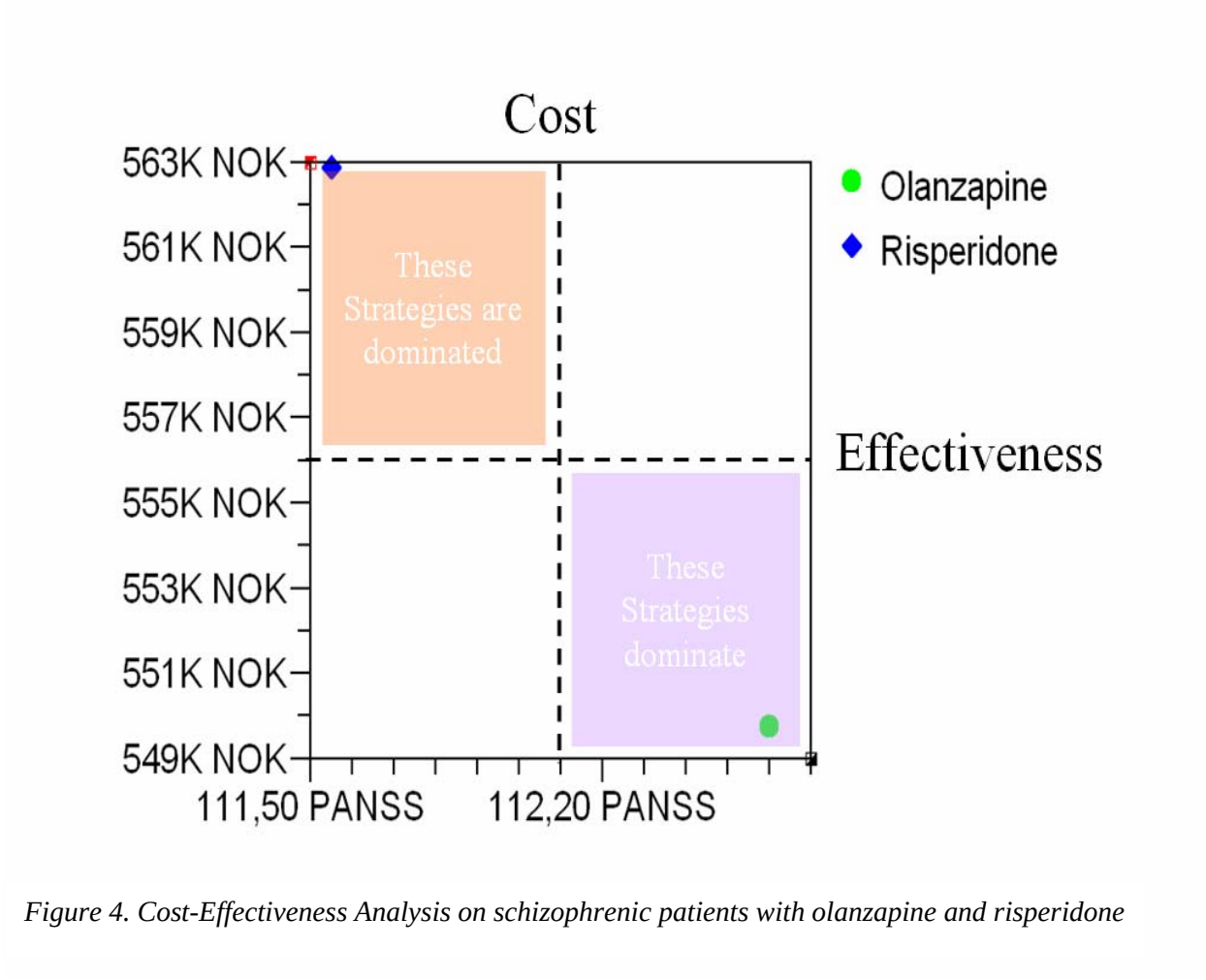


Figure 4. Cost-Effectiveness Analysis on schizophrenic patients with olanzapine and risperidone

5.2. Sensitivity analysis

Although the Cochrane meta-analysis provided the most of data used in the model, several parameters of probability and cost still seemed to contain uncertainty, especially, the parameters which were estimated by experts' opinion or assumed. Sensitivity analysis was aimed at firstly identifying and representing factors involved with uncertainty. Secondly, it was aimed at finding the most sensitive variables and reporting the weakness of the model. The third was to test impacts of difference between the adequate and mild respond to the antipsychotics in the model to glance schizophrenic patients with adequate respond in the real practice. Lastly, PSA using Monte Carlo simulation was conducted to report incorporative results involving all of the uncertain parameters.

5.2.1. One-way sensitivity analysis

In the model, the probability of acute relapse to compliant patients with olanzapine (P=0.098) was relatively high to the probability of acute relapse to compliant patients with risperidone (P=0.365) in the first year. To examine the sensitivity of the probabilities, one-way sensitivity analysis was conducted within a range of the acute relapse rate, 0.00 to 0.50. The amount of WTP was assumed to be NOK 5,000. One-way sensitivity analysis on the probability of acute relapse to compliant patients with olanzapine resulted in no a crossing point, *threshold* that represents a change in the optimal strategy in the NMB-the probability plane (Figure 4). One-way sensitivity analysis on the probability with risperidone resulted also the NMB-the probability plane with no threshold point. As a result, it was concluded that the probabilities of acute relapse to compliant patients with olanzapine and risperidone do not change the optimal alternative in the model.

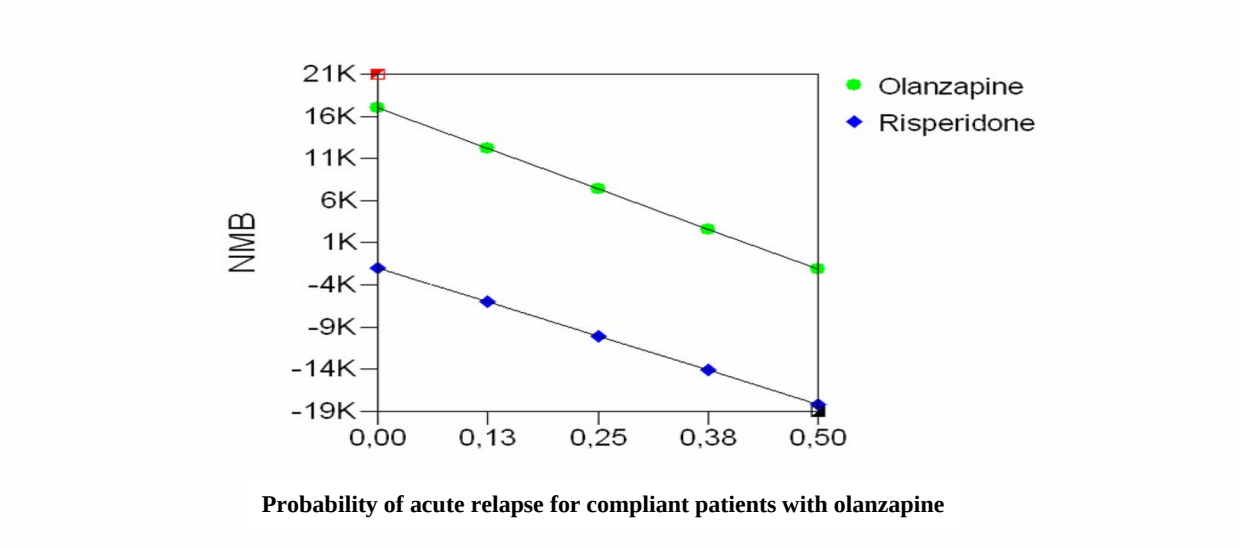


Figure 5. One-way sensitivity analysis on the probability of acute relapse to compliant patients with olanzapine (WTP=5,000), NMB refers to [Equation 2]

One-way sensitivity analysis examined other variables which referred to estimates or assumptions in other studies. The probability of acute relapse to noncompliant patients with olanzapine, the probability of acute relapse to noncompliant patients with risperidone and the probability of hospitalized care were tested but threshold points were not found, either. All of the results with the variables are summarized in a Tornado gram (Appendix V).

5.2.2. Tornado diagram

As a set of one-way sensitivity analyses, Tornado diagrams compare each impact of costs and probability parameter on the results. Figure 6 includes the relevant cost parameter in the first year where low and high input were set by +/- 30% of the cost estimates. Considering the potential of overestimating, differently with the drop out cost parameter, the low input was half of the drop out cost and the high input was the drop out cost value itself. The wide bars indicate that the variables have a large potential effect on the expected values of in the model. The result is summarized in Table 13 ranked with the ten broadest spread of cost parameters.

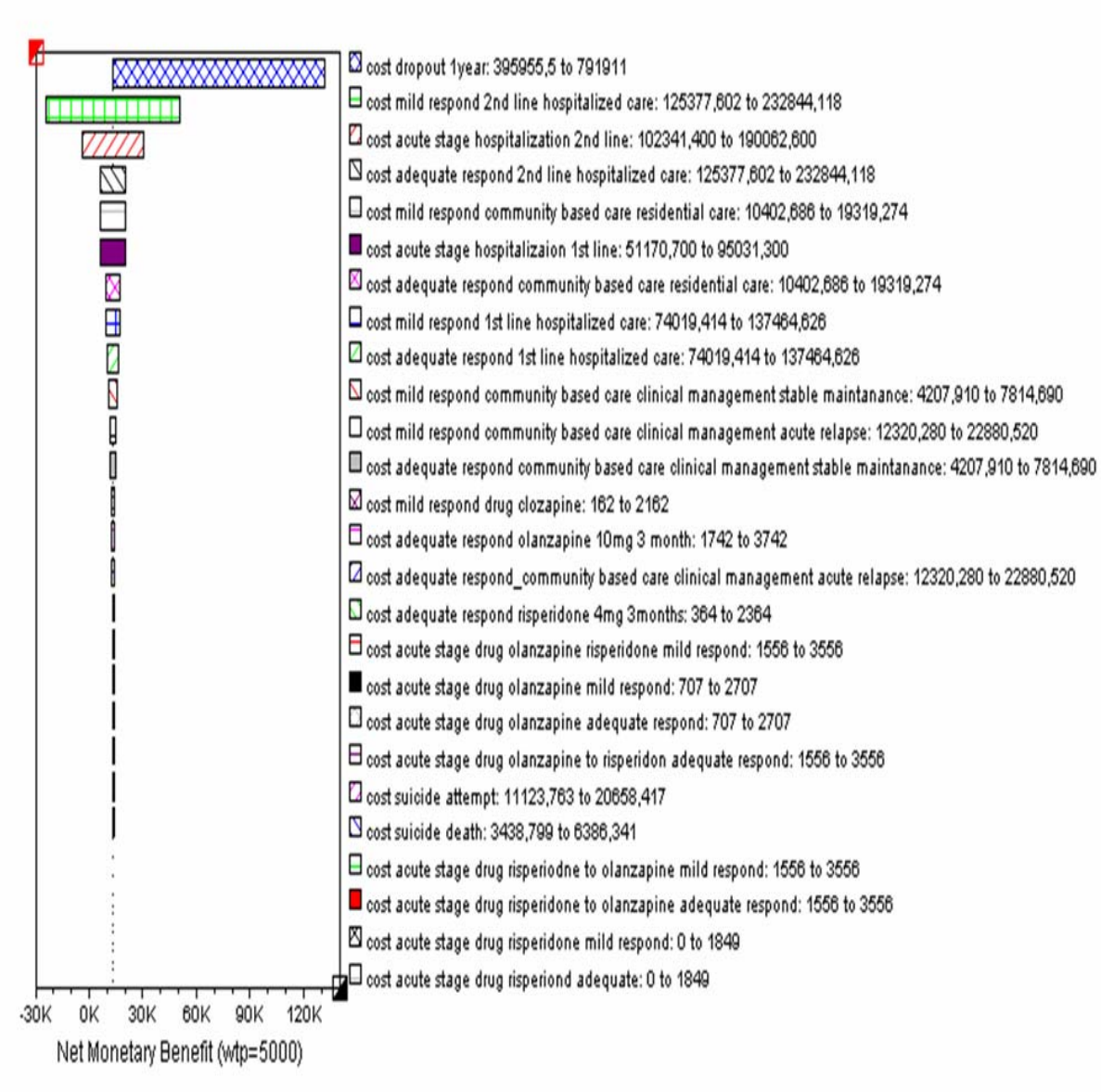


Figure 6. Tornado diagram with cost parameters in the first year, WTP=5,000 (NOK in 2008)

Table 13. Cost parameters ranked by the ten broadest spread in the first year, WTP=5,000 (NOK in 2008)

Rank	Parameters	Low Input	High Input	Spread
1	Cost dropout first year	395,955	791,911	118,186
2	Cost mild respond 2nd line hospitalized care	125,377	232,844	74,696
3	Cost acute stage hospitalization 2nd line	102,341	190,062	33,853
4	Cost adequate respond 2nd line hospitalized care	125,377	232,844	14,257
5	Cost mild respond community based care residential care	10,402	19,319	14,061
6	Cost acute stage hospitalization 1st line	51,170	95,031	13,842
7	Cost adequate respond community based care residential care	10,402	19,319	7,774
8	Cost mild respond 1st line hospitalized care	74,019	137,464	7,692
9	Cost adequate respond 1st line hospitalized care	74,019	137,464	5,591
10	Cost mild respond community based care clinical management stable maintenance	4,207	7,814	4,426

* A list with all of the cost parameters is presented in Appendix VI.

Among the cost parameters, the drop out cost had the largest impact on the results in the first year. However, the size of the drop out cost did not vary the optimal alternative in this study. In a one-way sensitivity analysis on drop out cost (Figure 7), the incremental cost between olanzapine and risperidone is gradually becoming smaller as corresponding the drop out cost becomes lower. However, even if the drop out cost is zero, the incremental cost was NOK 2,643 (Table 14) and risperidone is a still dominated by olanzapine.

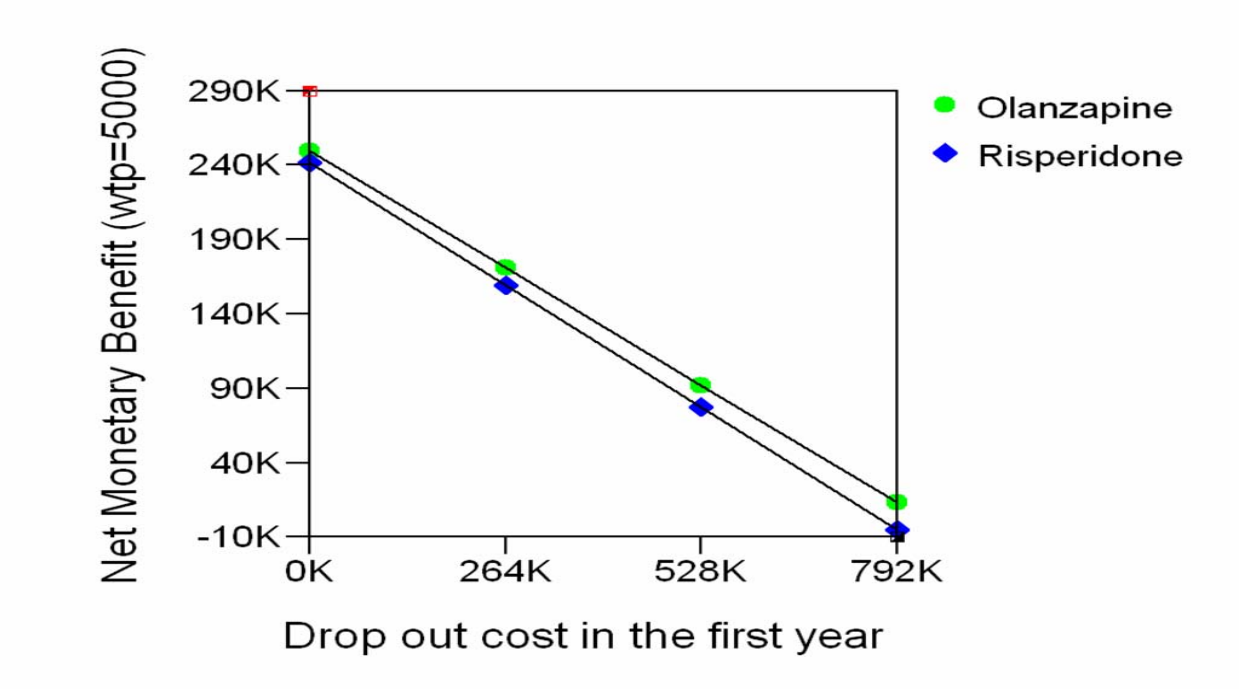


Figure 7. One-way sensitivity analysis on the drop out cost in the first year, WTP=5,000 (NOK in 2008)

Table 14. One-way sensitivity analysis on the drop out cost in the year, WTP=5,000 (NOK in 2008)

Drop out cost	Strategy	Cost	ΔC	Effectiveness	ΔE	ICER
0	Olanzapine	313,368	-	112.60	-	-
	Risperidone	316,011	2,643	111.55	-1.05	Dominated
158,382	Olanzapine	360,643	-	112.60	-	-
	Risperidone	365,383	4,740	111.55	-1.05	Dominated
475,147	Olanzapine	455,192	-	112.60	-	-
	Risperidone	464,127	8,935	111.55	-1.05	Dominated
791,911	Olanzapine	549,740	-	112.60	-	-
	Risperidone	562,871	13,131	111.55	-1.05	Dominated

In the Tornado diagram with the cost parameters, the cost for 2nd line hospitalized care in the maintenance stage appeared as the second most influential parameter to vary results. The following parameters are presented in ascending order; the 2nd line hospitalization in the acute stage, CBC residential care, 1st line hospitalized care in the maintenance stage, CBC stable maintenance care and CBC acute relapse care. Given the threshold of NOK 5,000, none of the cost parameters in the Tornado diagram in Figure 6 implied to switch the optimal alternative

Spreads of drug costs were quite small relatively to the other parameters (Figure 5). This result accorded with previous reports that the inpatient costs accounted for 78 to 94% of total treatment costs (98) and about 75% of the costs of schizophrenia treatment were due to inpatient or residential care, while drugs represent less than 5% (99).

Among probability parameters in the first year of the model, the drop out probability for olanzapine and the drop out probability for risperidone had the first and second most influence (table 15). The difference between low and high input of the range with probability parameters was 0.2 or 0.3.The Tornado diagram with probability parameters brought the results with threshold points. The threshold points were marked as black lines in the bars to indicate shifting points to an option with the highest net monetary benefits (Figure 8).

Table 15. Probability parameters ranked by the ten broadest spread in the first year, WTP=5,000 (NOK in 2008)

Rank	Parameters	Low Input	High Input	Spread
1	Probability risperidone drop out	0.1	0.3	9,731,224
2	Probability olanzapine drop out	0.1	0.3	9,236,100
3	Probability olanzapine adequate respond	0.1	0.3	6,185,932
4	Probability olanzapine inadequate respond	0.4	0.6	4,904,604
5	Probability risperidone adequate respond	0.1	0.3	4,062,491
6	Probability risperidone inadequate respond	0.4	0.6	3,896,226
7	Probability olanzapine intolerable adverse events	0.0	0.2	3,554,748
8	Probability risperidone intolerable adverse events	0.0	0.2	2,476,877
9	Probability risperidone suicide attempt	0.0	0.2	1,787,497
10	Probability clozapine suicide attempt	0.0	0.2	1,444,414

* A list with all of the probability parameters is represented in Appendix VII.

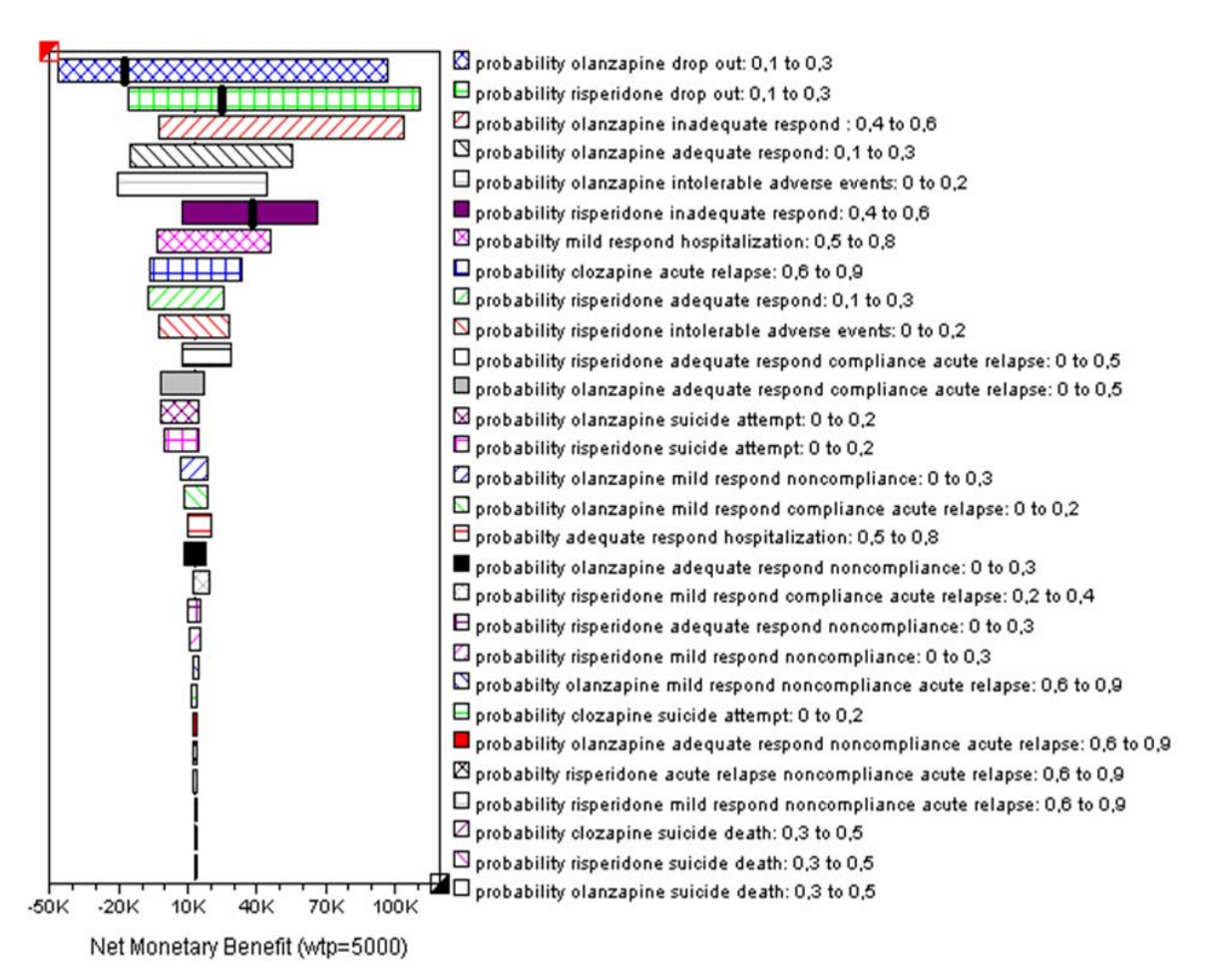


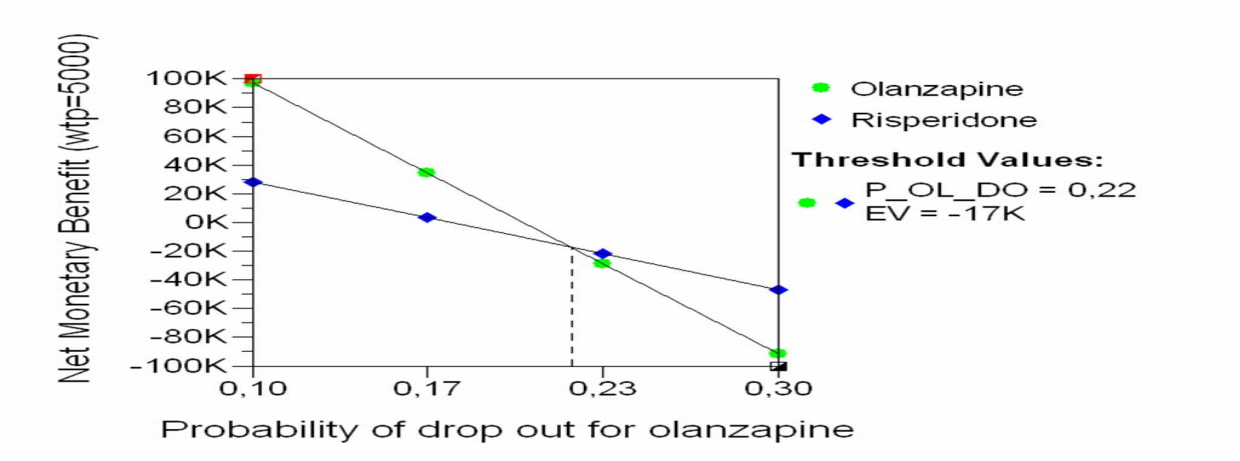
Figure 8. Tornado diagram with probability parameters in the first year, WTP=5,000 (2008 in NOK)

The following three probability parameters included threshold points switching the optimal alternative; drop out for olanzapine, drop out for risperidone, and inadequate respond for risperidone (Table 16).

Table 16. Summary of results of one-way analysis on probability analysis

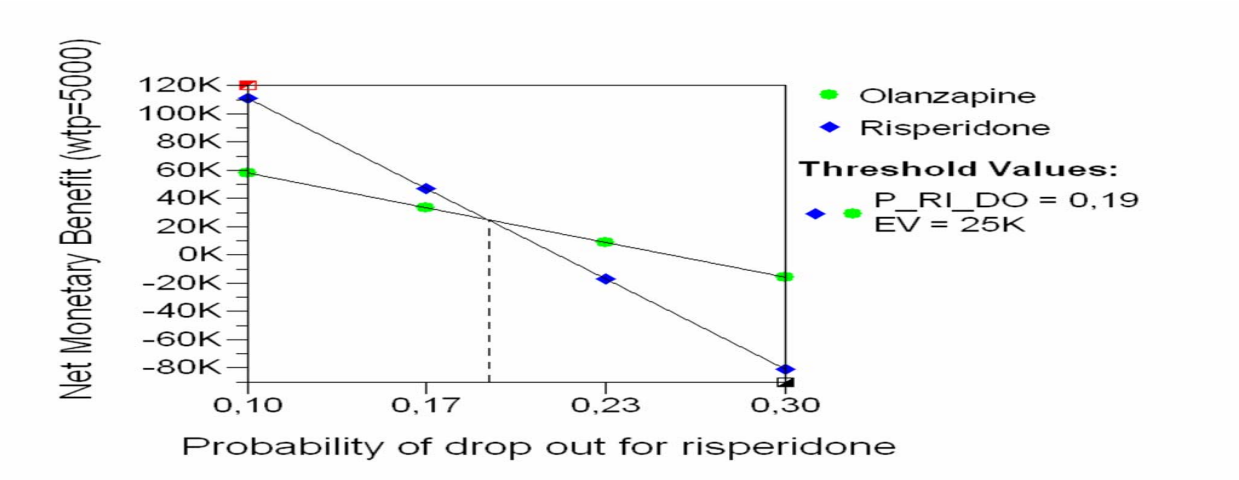
Parameter	Range	Threshold	Optimal alternative
Probability of drop out for olanzapine	0,10-0,30	0,22	Olanzapine: 0.10-0.22 Risperidone: 0.22-0.30
Probability of drop out for risperidone	0,10-0,30	0,19	Risperidone: 0.10-0.19 Olanzapine: 0.19-0.30
Probability of inadequate respond for risperidone	0,40-0,60	0,47	Risperidone: 0.40-0.47 Olanzapine: 0.47-0.60

In the one-way sensitivity analysis on the probability of drop out for olanzapine, olanzapine has the highest net benefit between 0.10 and 0.22, risperidone has the highest net benefit between 0.22 and 0.30 (Figure 9.1). In the one-way sensitivity analysis on the probability of drop out for risperidone, risperidone has the highest net benefit between 0.00 and 0.19, while olanzapine has the highest net benefit between 0.19 and 0.30 (Figure 9.2). Lastly, in the one-way sensitivity analysis on the probability of inadequate respond for risperidone, risperidone has the highest net benefit between 0.40 and 0.47, while olanzapine has the highest net benefit between 0.47 and 0.60 (Figure 9.3).



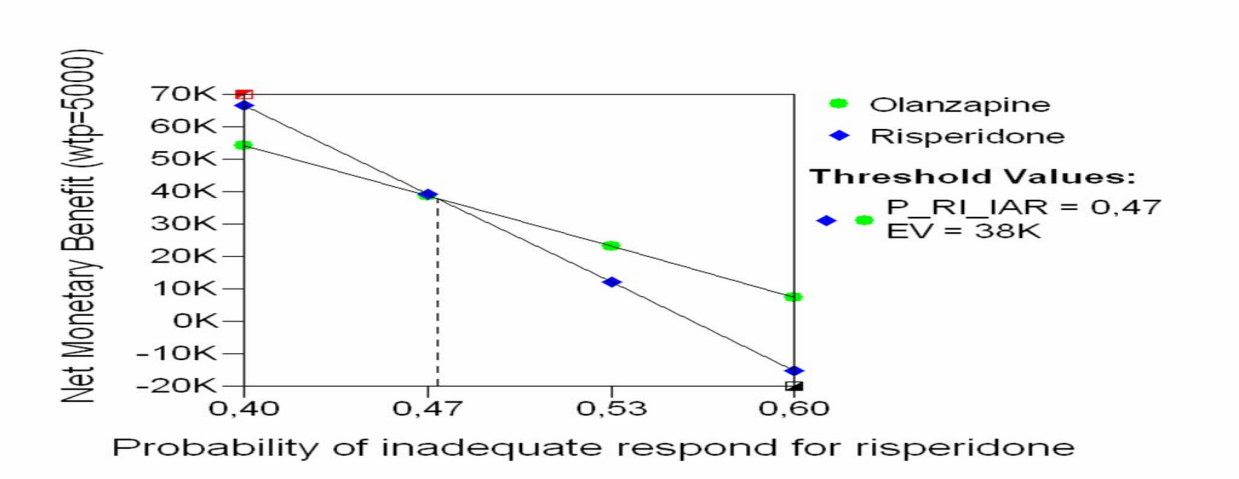
*P-OL-DO: Probability of drop out for olanzapine / *EV: expected value

Figure 9.1. One-way sensitivity analysis on the probabilities of drop out for and olanzapine, NMB (WTP=5,000)



*P-RI-DO: Probability of drop out for risperidone

Figure 9.2. One-way sensitivity analysis on the probabilities of drop out, risperidone, NMB (WTP=5,000)



*P-RI-IAR: Probability of inadequate respond for risperidone

Figure 9.3. One-way sensitivity analysis on the probabilities of inadequate respond for risperidone, NMB (WTP=5,000)

In general, the results presented in the Tornado diagram from the second to fifth year were nearly similar with the results from the first year. The text report of the Tornado diagram with cost and probability parameters from the second to fifth year is represented in Appendix VIII. The drop out cost for 4 years appeared as the parameter having the highest impact on the results but did not include the threshold points. Hence, olanzapine still dominated risperidone. The

results from the one-way sensitivity analysis of the following three probabilities; the probability of drop out for olanzapine, the probability of drop out for risperidone and the probability inadequate respond for risperidone, are presented in Appendix IX.

5.2.3. Two-way sensitivity analysis

Two-way sensitivity analysis was used to examine the impact of simultaneous changes in the values of two variables. Figure 10 shows the result of the two-way sensitivity analysis on the probability of drop out for olanzapine and the probability of drop out for risperidone in the first year. The planes occupied by discreet colors indicated the chance for alternatives to be optimal with the highest NMB. So, since risperidone occupies more than half of the plane in the graph, it was interpreted that if the probability of drop out for risperidone is the same or even slightly higher than that for olanzapine, risperidone is an optimal alternative with the highest NMB.

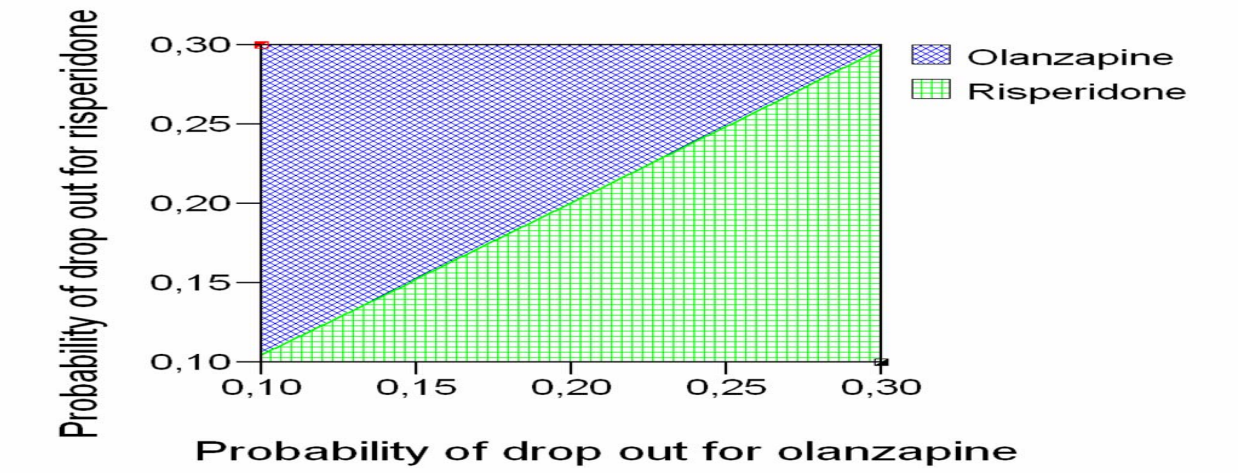


Figure 10. Two-way sensitivity analysis on the probability of drop out for olanzapine and the probability of drop out for risperidone in the first year, NMB (*WTP=5,000*)

5.2.3. One-way sensitivity analysis on adequate respond parameters

In model, the treatments responds were defined into three different sub-responds; adequate, mild and inadequate. Since the inadequate respond, along with the intolerable adverse events, was a pathway forward to switching to the 2nd or 3rd line treatment, the role of inadequate respond was discreet to that of adequate and mild respond. However, because there was no difference made in further branches' probability and cost parameters of between adequate and mild respond, the

role of adequate and mild respond were not discreet in the model. Hence, one-way sensitivity analysis varied values of parameters with the adequate respond which were initially recorded same as parameters with the mild respond and examined the changes on the results.

One-way sensitivity analysis examined the cost parameter of hospitalized care for the 1st line respondent with the adequate respond in the maintenance stage (Figure 11). Risperidone is an optimal alternative with the highest NMB, under the condition that the costs of hospitalized care for the 1st line respondent with the adequate respond are less than NOK 40,000 which are equivalent to the total costs of 5.14 days hospitalized care including post hospital CBC and post hospital residential care. Initially, the length of hospitalization for the 1st line respondent and the 2nd line respondent were 30 days and 60 days, respectively (Table 9).

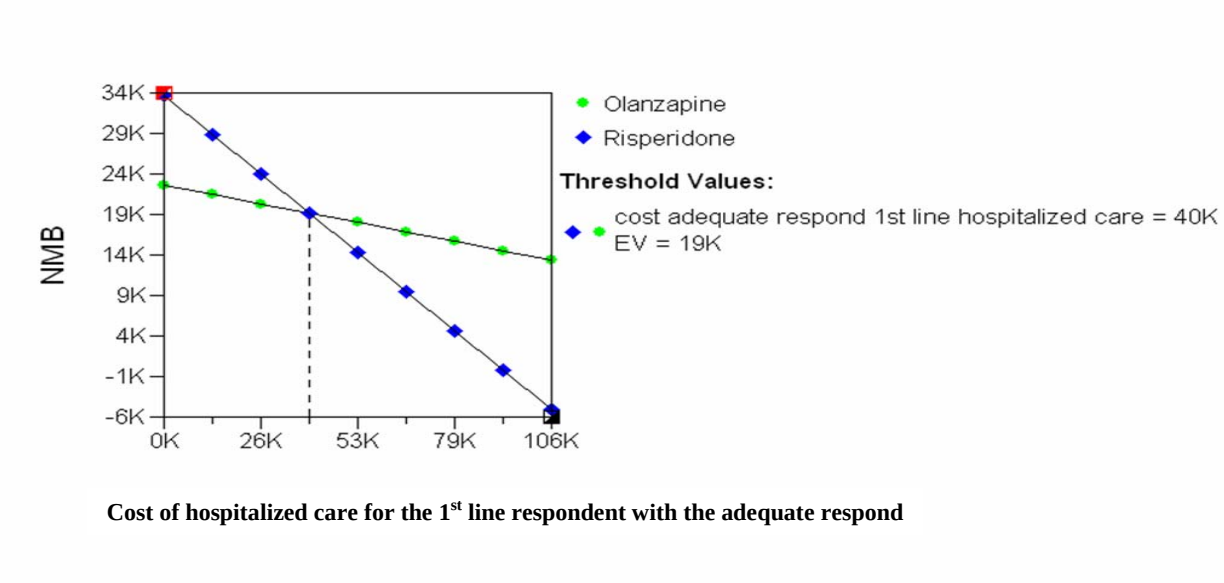


Figure 11. One-way sensitivity analysis on cost of hospitalized care for the 1st line respondent with the adequate respond, NMB (WTP=5,000)

However, one-way sensitivity analysis for the cost parameter of hospitalized care for the 2nd line respondent with the adequate respond did not result in threshold points. (Appendix X). The one-way sensitivity analysis examined the other parameters involved with adequate respond; the cost of CBC non-hospital relapse management for the adequate respondent, the probability of noncompliance for adequate respondent, the probability of acute relapse to the compliant patient with the adequate respond, the probability of acute relapse to the noncompliant patient with the

adequate respond and the probability of acute relapse for the adequate respondent. The results came out with no change in the optimal alternative, either.

5.3. Probability Sensitivity Analysis using Monte Carlo simulation

In this study, all of the cost and probability parameters were incorporated into the PSA using Monte Carlo simulation and the parameters were defined in as probability distributions to reflect their uncertainty. The probability parameters which referred to the Cochran meta-analysis were defined as *beta distribution, integer form* and the probability parameters, which referred to expert's opinion or estimates were defined as *beta distribution, real number form* or *uniform distribution*. Also, the cost parameters were defined as *uniform distribution* or *gamma distribution*. The input parameters in the PSA are summarized with the type of distribution and their values in Appendix XI and XII. In the PSA, Monte Carlo simulation propagated input parameters 2,000 times within randomly sampled from the probability distributions and produced in following results.

The 2,000 pairs of the total cost and effectiveness with olanzapine and risperidone were quite widely scattered. The mean total cost for olanzapine at the first year was NOK 494,897 and it was still lower than the mean total cost for risperidone at the first year (NOK 502,704). The mean PANSS reduction for olanzapine was 0.91 higher than risperidone. However, with 95% confidence interval, the total cost for olanzapine was NOK 342,807 to 706,504 and the total cost for risperidone was NOK 344,428 to 725,844. The effectiveness of olanzapine was 105 to 120 and that of risperidone was 104 to 120 (Table 17).

Table 17. The PSA results with cost (NOK in 2008) and effectiveness (the PANSS reduction)

	Costs (mean)	Effectiveness (mean)
Olanzapine	342,807 – 706,504 (494,897)	105 – 120 (112.79)
Risperidone	344,428 – 725,844 (502,704)	104 – 120 (111.88)

* 95% confidence level: 2.5% - 97.5%

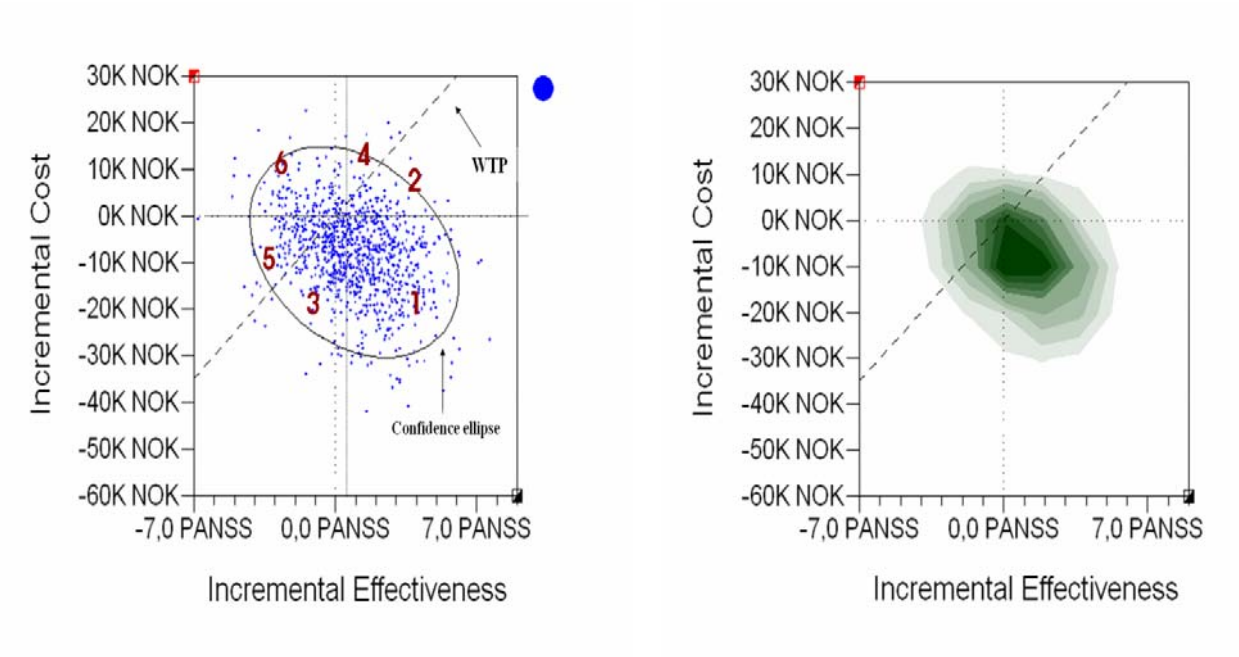
The ICE scatterplot was conducted to visualize the spread of pairs of incremental cost and effectiveness values from the simulation results in the PSA. As a setting of ICE scatterplot with

95% confidence interval, the comparator was olanzapine and the baseline was risperidone. In the incremental cost-effectiveness plane when WTP is NOK 5,000 (Figure 12), 1,151 points (55.55%) belonged to *Section 1* (Table 18) which the olanzapine dominates risperidone (referred to Figure 2). 482 points (24.0%) belonged to *Section 5* which the risperidone is an optimal alternative. 183 points (9.2%) belonged to *Section 2* which the olanzapine is cost effective. 179 points (9.0%) belonged to *Section 6* which risperidone dominates olanzapine. The rest of the pairs (0.3%) belong to *Section 3* which olanzapine is optimal

Table 18. The PSA results with the ICE Scatterplot (*Number of sample=2,000*, *WTP=5,000*)

Section	1	2	3	4	5	6	Indifference
Points (N)	1,151	183	5	0	482	179	0
Percent (%)	57.6	9.2	0.3	0.0	24.1	9.0	0

In summary, the chance of olanzapine being an optimal alternative in the model is 67.1% (sum of points in *Section1 to 3,* where the comparator is chosen as an optimal alternative). The ICE isocontours graph shows the relative concentration of points in the scatterplot (Figure 12).



* Cost tolerance (+/-): 1, Effect tolerance (+/-): 0.01

Figure 12. ICE Scatterplot of Olanzapine vs. Risperidone, and the ICE isocontours graph (WTP=5,000)

Chapter 6

DISCUSSION AND CONCLUSION

One of the strengths in the decision analytic model was to embrace critical factors in modelling schizophrenia. Martin Knapp pointed out follow three factors as mostly influencing costs of schizophrenia; *non-adherence to medication*, *relapse* and *in-patient admissions* (100). In a review of pharmacoeconomic modelling in schizophrenia (72), following confounding factors which increase or decrease the ICE and the ICER were suggested; *relapse*, *compliance*, *institution*, *drop out* and *switch*. In this study, the model involved all of those factors together with other important factors, such as different degree of responds to the antipsychotics, adverse events and suicide risk. Another strength was to preserve objectivity with the methods that most of the data on probability and effectiveness were based on the extensive meta-analysis. The third was that the model presented the incorporative results involving uncertainty surrounding all parameters by the PSA using Monte Carlo simulation.

The results of this study were compared with other CEAs of olanzapine and risperidone, which were reported by a systematic review (40). Palmer 1998 (76), De Hert 2000 (101) and Almond 2000 (102) analyzed the cost-effectiveness by means of a Markov model and concluded that olanzapine was more costly than risperidone; however, olanzapine considered to increase effectiveness at reasonable cost. Kasper 2000 (103), Loos 2000 (104) and Martin 2000 (105) concluded that olanzapine was more cost-effective than risperidone and Edgell 2000 (106) argued that olanzapine dominated risperidone. On the other hand, Bille 1999 (107) and Duchesne 1999 (108) reported that risperidone more cost-effective than olanzapine.

The most problematic issue of the model was probably to refer to German experts' opinion for proportion of use, for example, the number of visit to psychiatrist and/or psychologist, GP and out patient clinic in CBC, and the proportion of use in the residential care and the probability of hospitalized care. Although one-way sensitivity analysis and the PSA examined the uncertainty with the values referred, it might still be the most severe weakness in the model. Further studies will have to verify the feasibility of adapting the sources estimated in Germany. Another issue is population characteristics in the clinical trials. In this study, the effectiveness of the

antipsychotic referred to Conley 2001 (71) (n=497; M=274/F=103) and Jeste 2003 (78) (n=175; M=64/F=113) and the probability of acute relapse was based on Namjoshi 2002 (94) (n=364; M=259/F=105). All of those studies were randomized and double-blind clinical trials in the United States. However, while the mean age of the Conley study group was 39.9 years (SD=11) and that Namjoshi study group was 39.4 years, the mean age of the Jeste study group was over 71 years. Since Jeste and his colleges aimed to study risperidone and olanzapine in elderly patients with schizophrenia and schizoaffective disorder, the single use of effectiveness data from the Jeste's study seemed doubtful to generalize into the population with schizophrenia in Norway.

The olanzapine and risperidone seemed the appropriate comparators as the most frequently prescribed for schizophrenia in Norway. Based on Norwegian Prescription Database in 2007, olanzapine was used by 15,637 users which was the highest number of the users among antipsychotics for schizophrenia treatment and quetiapine (n=8,310), risperidone (n=7,891), haloperidol (n=4,803), zuclopenthixol (n=3,196) and clozapine (n=2,098) followed after in Norway (9). Quetiapine, which is an atypical antipsychotic used in the management of schizophrenia and bipolar I disorder, and used off-label for a variety of other purposes, including insomnia and anxiety disorders, was also regarded as a popular alternative for schizophrenia treatment in Norway. So, further extended studies including other alternatives for schizophrenia are needed to capture overall antipsychotic medication practice in Norway.

The decision analytic model also has limits. In the maintenance stage, there was no way out of the 3 months cycle except ending in suicide death. However, it might have been more realistic if the model had terminal nodes including comorbidity with schizophrenia. The percentage of people with schizophrenia showing at any point in time clinically significant depressed mood is at least 25% (109) and the patients experiencing depression when in remission from a psychotic episode, at a time of increasing insight into their illness, are at high risk of suicide (13). Beside, lifetime prevalence of substance abuse or dependence in persons with schizophrenia has been estimated at over 30% for alcohol and around 25% for illicit drugs in the United States (110) and the impact of comorbidity with substance abuse is significant in reducing treatment effectiveness, worsening positive psychotic symptoms, increasing social disability and raising

the likelihood of violence (111). Cardiovascular diseases and HIV infection also has reported with increasing frequency, prevalence rates in schizophrenia patients (13). A model of antipsychotic medications for schizophrenia including comorbidity might bring out increased total costs per schizophrenic patient due to other illness caused it would decrease the value of NMB.

According to HTA reports on antipsychotics for schizophrenia (40), the antipsychotics cause various types of side effects such as movement disorders, sedation, autonomic effects, gastrointestinal effects, weight gain, prolactin-related problems and cardiotoxic effects. According to the Cochrane meta-analysis (1), risperidone caused significantly more following side effects; insomnia, headache, constipation, abnormal ejaculation, agitation and backache. Olanzapine caused significantly more dry mouth[15] and in terms of gain weight, olanzapine resulted in the twice higher chance of gaining weight in both short term and long term clinical trials than risperidone. In this study, the model included only EPSs as side effects caused by the antipsychotics. The WHO schizophrenia report suggested only EPSs as the side effect represented serious problems and deserved special attention while the most of the side-effects are mild and time-limited (13). However, it might be still necessary to include other side effects as long as they appear with significant difference between olanzapine and risperidone, in order to perform such a limited project which requires identifying delicate differences.

This study has also following issues in identifying costs for schizophrenia patients. The model has risk to underestimate the costs for schizophrenic patients because not only with the problem to include all of the different treatments for schizophrenia but difficulty to update all of the newly introduced treatments in Norway. In 2001, *Day treatments* and *home care* for any kind of illness occupied 8.6% of the total health expenditure in Norway (112). The cost of day treatment for schizophrenic patients could refer to the partial sheltered accommodation (2) but the cost data of home care services offered by both public and private providers were not available in Norway. In addition, to comply with the economic principle measuring cost as *opportunity cost*[16], it might be necessary to include the cost for the voluntary services for schizophrenia in

[15] *Xerostomia* is a medical term for dry mouth.
[16] Opportunity cost or economic opportunity loss is the value of the next best alternative foregone as the result of making a decision (105).

Norway. For example, the opportunity cost of a counselor who volunteers services to a schizophrenia treatment could be the salary earned in a paid position.

Second, the costs estimated in 1999 were likely to differ with the actual cost in 2008 due to changes having been introduced in the mental health service environment. In Norway, like the most western countries, the services for people with mental health problems have gone through major changes over the last decades (113). In 1998, the Norwegian Parliament introduced a national mental health programme, calling for a major increase in the funding of mental health related services as well as a major reorganization of these services and implementation of the programme took place between 1999 and 2008 (114). The increase in the funding would expand the total volume of health resource consumed for mental patients, perhaps schizophrenia patients as well. Another main change in the mental health care in Norway was that the reorganization, which was aimed at strengthening community based services and diversifying the contents of those services for sufficient preventive measures and planning, coordination and monitoring on discharge follow-ups for mental patients, was likely to magnify expenses in community based care for schizophrenia in Norway. However, the reorganization not necessarily reduced hospital wards and specialized care for psychiatric patients, rather those institutions had been expanded as mental health services were lacking at all level and accessibility to specialized services was inadequate and inpatient stays were often too short (106). Furthermore, a factor to alter mostly the environment of mental health services might be a series of wide-ranging reforms designed to make greater use of market mechanisms in health care system in Norway. For example, competition has been introduced among health care providers by controlling the DRG base reimbursement and block grants and the number of contracts between municipalities and private health providers have been increased. Also out-of-pocket payments have gradually raised and private insurance newly entered the health care industry in Norway. Hence, applying inflation rate with CPI was a limited method to reflect all of the changes which might have varied costs of schizophrenia treatment services in Norway.

Third, the total expected cost per schizophrenic patient would be more extensive with a patient/family perspective of or a societal perspective since these perspectives should be concerned with indirect costs of schizophrenia. While direct costs associated with schizophrenic

patients were NOK 1.8 million, indirect costs associated with schizophrenic patients were NOK 1.7 million in Norway (7). The indirect costs were based on the finding that 80% of patients with schizophrenia were without regular work while the 20% would work if they had not had this disease (99) but the amount could have been more if other issues surrounding schizophrenia were included as Martin Knapp argued that hidden costs to people with schizophrenia themselves, to their families and caregivers and to society are often substantial (100). Not only financial losses such as out of pocket payments for treatment, transport costs and lost income due to employment difficulties but social disability, social stigma[17] and burden on caregivers could be considered as substantial costs. Considering the potential of the indirect cost, the total expected costs per schizophrenic patients in the model were perhaps a tip of iceberg.

Finally, cost-effectiveness analysis is limited with a basic form of measuring health consequences of a programme as specific units such as the PANSS. Because the measure of primary effectiveness may differ from programme to programme, cost-effectiveness analysis can not be used to make comparisons across a broad set of interventions (68). Moreover, a more critical issue is whether the specific measuring unit is indeed equivalent to a purpose of introducing the health programme or not. Therefore, in this study, accordance of the PANSS reduction to utility of the schizophrenic patients is a matter of the utmost concern to assess whether the results based on NMB/WTP produced by the model are valuable or not. In fact, health state preferences of patients for schizophrenia were measured by a standard gamble approach (115) but only few data were available on utility weights for health states specific to the area of schizophrenia (75). However, mostly, the PANSS along with measurements for side effects seemed exchangeable with quality of life (QOL). In a conceptual modelling study, the author argued appropriate conceptual models of QOL for schizophrenia could be developed with standardized scales including the PANSS, abnormal involuntary movements scale (AIMS), Hillside Akathisia scale (HAI), and the social performance schedule (SPS) (116). Leslie and colleagues suggested that utility mapping function with schizophrenia could be created by using the PANNS and a set of health states including the presence of common adverse effects of medication (117). In their study of estimating utility gains with effective treatment of

[17] Social stigma refers to a set of deeply discrediting attributes, related to negative attitudes and beliefs towards a group of people, likely to affect a person's identity and thus leading to a damaged sense of self through social rejection, discrimination and social isolation (Goffman, 1963)

schizophrenia (118), 36-Item Short-Form Health Survey (SF-36) and the Extrapyramidal Symptom Rating Scale (ESRS) were additionally used with the PANSS to measure movement disorder severity.

Considering all of the uncertainties surrounding the costs and effectiveness of the olanzapine and risperidone, the model could not conclude that olanzapine was more cost-effective than risperidone in Norway. For more precise results, further clinical trials are recommended to follow up patients who drop out of the study and evaluate relapse rates categorized into compliant and noncompliant patients distinctively. However, the model seemed capable to figure the overall total costs per schizophrenic patient treated with antipsychotic medications in Norway. In addition, the model can be used to provide a basic frame of modelling patients with schizophrenia diagnosis and to facilitate further schizophrenia studies.

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Appendix

[Appendix I] Diagnosis of schizophrenia in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)

A minimum of one very clear symptom belonging to any one of the groups listed below as (a) to (d) or symptoms from at least two of the groups referred to as (e) to (i) should have been clearly present for most of the time during a period of 1 month or more.

a) Thought echo, thought insertion or withdrawal and thought broadcasting.

b) delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions or sensations; delusional perception.

c) hallucinatory voices giving a running commentary on the patient's behaviour or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body.

d) persistent delusions of other kinds that are culturally inappropriate and completely impossible, such as religious or political identity, or superhuman powers and abilities (e.g. being able to control the weather or being in communication with aliens from another world).

e) persistent hallucinations in any modality, when accompanied either by fleeting or halfformed delusions without clear affective content or by persistent over-valued ideas, or when occurring every day for weeks or months on end.

f) breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms.

g) catatonic behaviour, such as excitement, posturing. or waxy flexibility, negativism, mutism and stupor.

h) 'negative' symptoms such as marked apathy, paucity of speech and blunting or incongruity of emotional responses, usually resulting in social withdrawal and lowering of social performance; it must be clear that these are not due to depression or neuroleptic medication.

i) a significant and consistent change in the overall quality of some aspects of personal behaviour, manifest as loss of interest, aimlessness, idleness, a self-absorbed attitude and social withdrawal.

[Appendix II] Diagnosis of schizophrenia in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)

A. Characteristic symptoms: Two or more of the following, each present for a significant portion of time during a 1-month period, or less if successfully treated: 1) Delusions, 2) Hallucinations, 3) Disorganized speech, e.g. frequent derailment or incoherence, 4) Grossly disorganized or catatonic behavior, 5) Negative symptoms, i.e. affective flattening, alogia or avolition. *Note*: Only one criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.

B. Social/Occupational dysfunction. For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic or occupational achievement).

C. Duration. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet criterion A, i.e. active-phase symptoms, and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in criterion A present in an attenuated form (e.g. odd beliefs, unusual perceptual experiences).

D. Schizoaffective and mood disorder exclusion. Schizoaffective and mood disorders have been ruled out because either (1) no major depressive, manic or mixed episodes have occurred concurrently with the active-phase symptoms or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.
E. Substance/general medical condition exclusion. The disturbance is not related to the direct physiological effect of a substance (e.g. a drug of abuse, a medication) or a general medical condition.

F. Relationship to a pervasive developmental disorder. If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

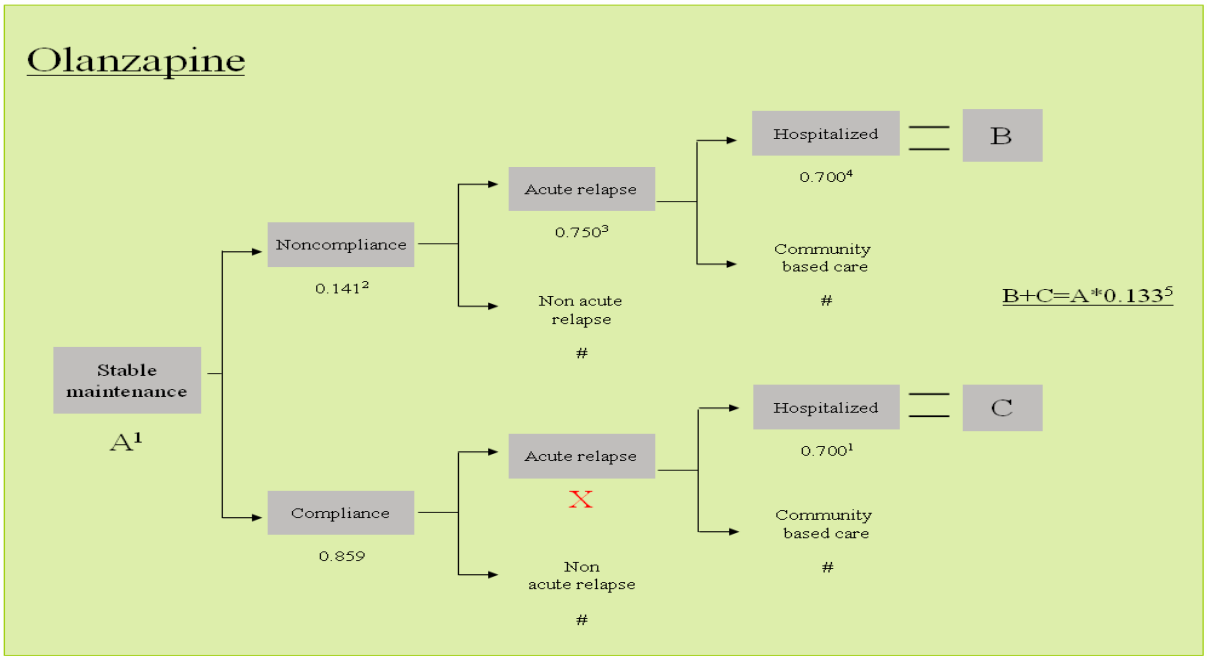
[Appendix III] A summary of studies used as source providing effectiveness and probabilities

Author/year	Population	Duration	Intervention	Allocation concealment
Chan 2003	N=60	8 weeks	1. Risperidone: dose range 0.5-6 mg/day. N=30.	B-Unclear
			2. Olanzapine: dose range 2.5-20 mg/day. N=30.	
Conley 2001	N=407	8 weeks	1. Risperidone: dose range 2-6 mg/day, mean 4.78 mg/day. N=188. 2. Olanzapine: dose range 5-20 mg/day, mean 12.43 mg/day. N=189.	A – Adequate
Harvey 2003	N=176	8 weeks	1. Risperidone: dose range 1-3 mg/day. N=87.	B-Unclear
			2. Olanzapine: dose range 5-20 mg/day. N=89.	
Jeste 2003	N=175	8 weeks	1. Risperidone: dose range 1-3 mg/day. N=87.	B-Unclear
			2. Olanzapine: lowest dose not stated, range ~5-20 mg/day. N= 88.	
Littrell 1999	N=24	one year	1. Risperidone: dose range 5.2 mg/day. N=12.	B-Unclear
			2. Olanzapine: dose range 19.2 mg/day. N=12.	
Ritchie 2003	N=66	4 weeks	1. Risperidone: dose not specified. N=32.	
			2. Olanzapine: dose not specified. N=34.	
Tran 1997	N=339	28 weeks	1. Risperidone: dose range 4-12 mg/day. N=167.	A-Adequate
			2. Olanzapine: dose range 10-20 mg/day. N=172.	
CATIE 2005	N=1460	52 weeks	1. Risperidone: dose 1.5 to 6mg/d. N=341.	B-Unclear
			2. Olanzapine: dose 7.5 to 30mg/day. N=336.	
			3. Quetiapine: dose 200 to 800 mg/day. N=337.	
			4. Perphenazine: dose 8 to 32 mg/day. N=261.	
			5. Ziprasidone: dose 40 to 160 mg/day. N=185.	
Keefe 2005	N=414	52 weeks	1. Risperidone: dose range 2-10 mg/day. N=158.	A-Adequate
			2. Olanzapine: dose range 5 to 20 mg/day. N=159.	
			3. Haloperidol: dose range 2-19mg/day. N=69.	
Purdon 1998	N=65	54 weeks	1. Risperidone: dose range 4-10 mg/day. N=21.	A-Adequate
			2. Olanzapine: dose range 5-20 mg/day. N=21.	
			3. Haloperidol: dose range 5-20 mg/day. N=23.	
Namjoshi 2002	N=364	52 weeks	1. Risperidone: dose range 2-10 mg/day. N=136.	B-Unclear
			2. Olanzapine: dose range 5-20 mg/day. N=143.	
			3. Haloperidol: dose range 2-9 mg/day. N=85.	

* Source: A systematic review; Risperidone versus olanzapine for schizophrenia (Cochrane 2005)

[Appendix IV] An explanatory estimating process for probabilities of acute relapse to compliant patients with olanzapine and risperidone

According to a clinical trial (94), 19 of 143 patients (13.3%) with olanzapine were hospitalized and 39 of 136 patients (28.7%) with risperidone were relapse/hospitalized by one year. I supposed that in the below figure, 13.3% of patients with olanzapine at the stable maintenance stage should be equal to the sum of the number of hospitalized patients with acute relapse to noncompliant patients with olanzapine (B) and the number of hospitalized patients with acute relapse to compliant patients with olanzapine (C). Suppose, the probability of acute relapse to compliant patients with olanzapine is X_1, then the following formula is made.

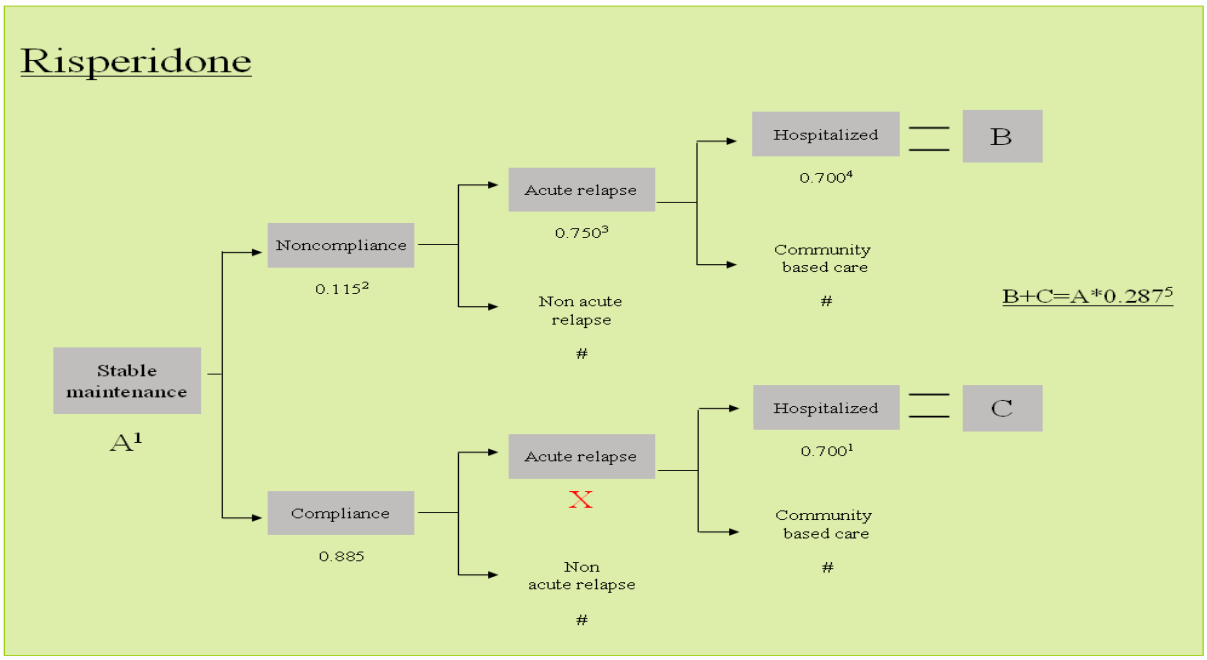


1. The number of patients in the stable maintenance.
2. The probability of noncompliance referred to (90), (91), (92), (51).
3. The probability of acute relapse to noncompliant patients with olanzapine referred to (77)
4. The probability of hospitalized care to referred to (75)
5. The probability of being hospitalized to patients with olanzapine (94).

B (=A*0.141*0.75*0.7) + C (=A*0.859*X_1*0.7) = A*0.133

So, X_1 = 0.098

Similarly, suppose, the probability of acute relapse to compliant patients with risperidone is X_2, then the following formula is made.



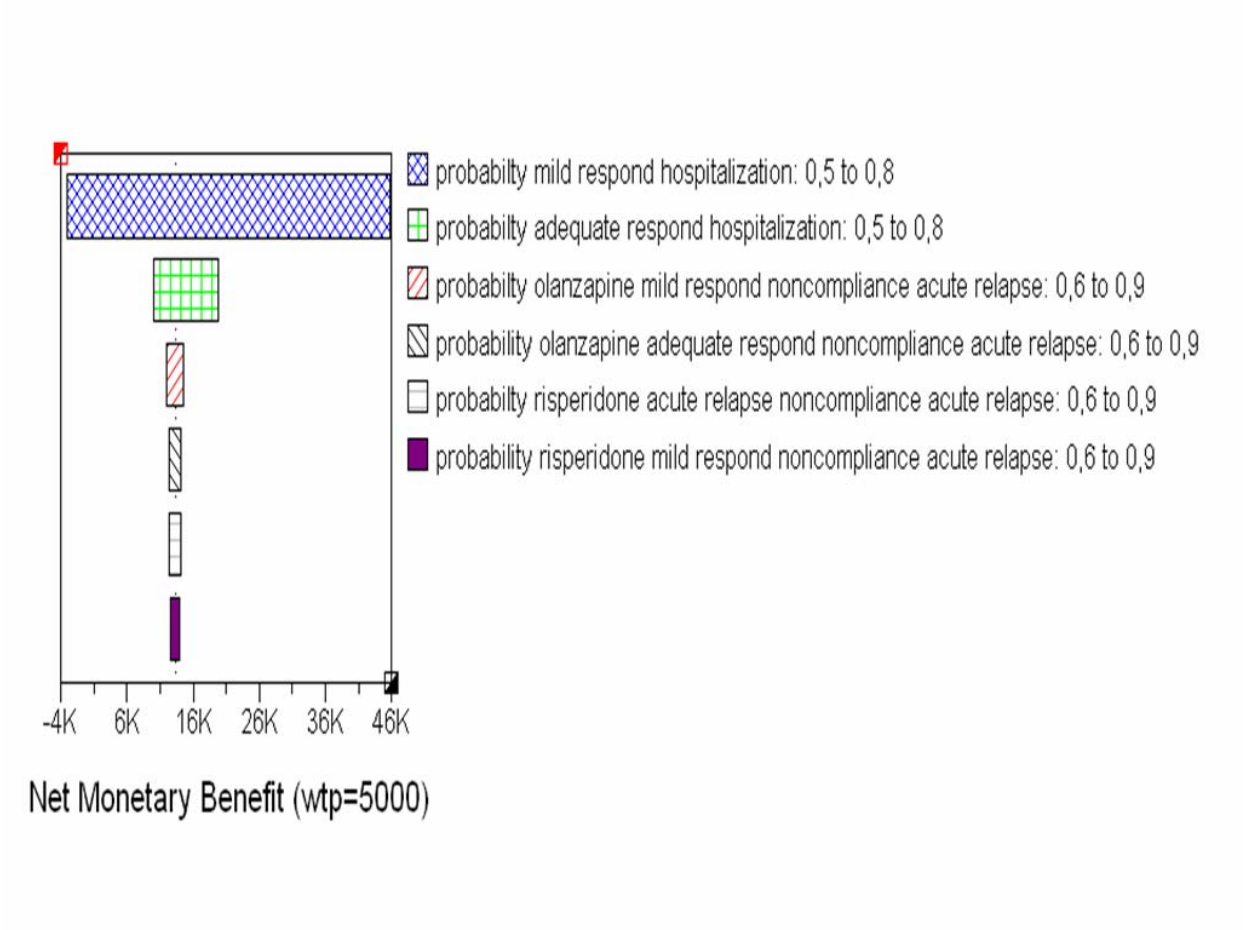
1. The number of patients in the stable maintenance.
2. The probability of noncompliance referred to (90), (91), (92), (51).
3. The probability of acute relapse to noncompliant patients with olanzapine referred to (77)
4. The probability of hospitalized care to referred to (75)
5. The probability of being hospitalized to patients with olanzapine (94).

B (=A*0.115*0.75*0.7) + C (=A*0.88*X_2*0.7) = A*0.287

So, X_2 = 0.365

Hence, the probability of acute relapse to compliant patients with olanzapine is 0.098 and the probability of acute relapse to compliant patients with risperidone is 0.365.

[Appendix V] Tornado diagram with estimated or assumed parameters



[Appendix VI] A list with all of the cost parameters in the first year in Tornado diagram (NOK in 2008)

Rank	Parameters	Low Input	High Input	Spread
1	Cost dropout first year	395,955	791,911	118,186
2	Cost mild respond 2nd line hospitalized care	125,377	232,844	74,696
3	Cost acute stage hospitalization 2nd line	102,341	190,062	33,853
4	Cost adequate respond 2nd line hospitalized care	125,377	232,844	14,257
5	Cost mild respond community based care residential Care	10,402	19,319	14,061
6	Cost acute stage hospitalization 1st line	51,170	95,031	13,842
7	Cost adequate respond community based care residential care	10,402	19,319	7,774
8	Cost mild respond 1st line hospitalized care	74,019	137,464	7,692
9	Cost adequate respond 1st line hospitalized care	74,019	137,464	5,591
10	Cost mild respond community based care clinical management stable maintenance	4,207	7,814	4,426
11	Cost mild respond community based care clinical management acute relapse	12,320	22,880	3,694
12	Cost adequate respond community based care clinical management stable maintenance	4,207	7,814	2,803
13	Cost mild respond drug clozapine	162	2,162	1,874
14	Cost mild respond drug olanzapine	1,742	3,742	1,458
15	Cost adequate respond olanzapine 10mg 3 month	1,742	3,742	1,060
16	Cost adequate respond, community based care clinical management acute relapse	12,320	22,880	999
17	Cost adequate respond risperidone 4mg 3months	364	2,364	622
18	Cost acute stage drug olanzapine risperidone mild respond	1,556	3,556	598
19	Cost mild respond drug risperidone	364	2,364	553
20	Cost acute stage drug olanzapine mild respond	707	2,707	365
21	Cost acute stage drug olanzapine adequate respond	707	2,707	265
22	Cost acute stage drug olanzapine to risperidone adequate respond	1,556	3,556	173
23	Cost suicide attempt	11,123	20,658	154
24	Cost suicide death	3,438	6,386	31

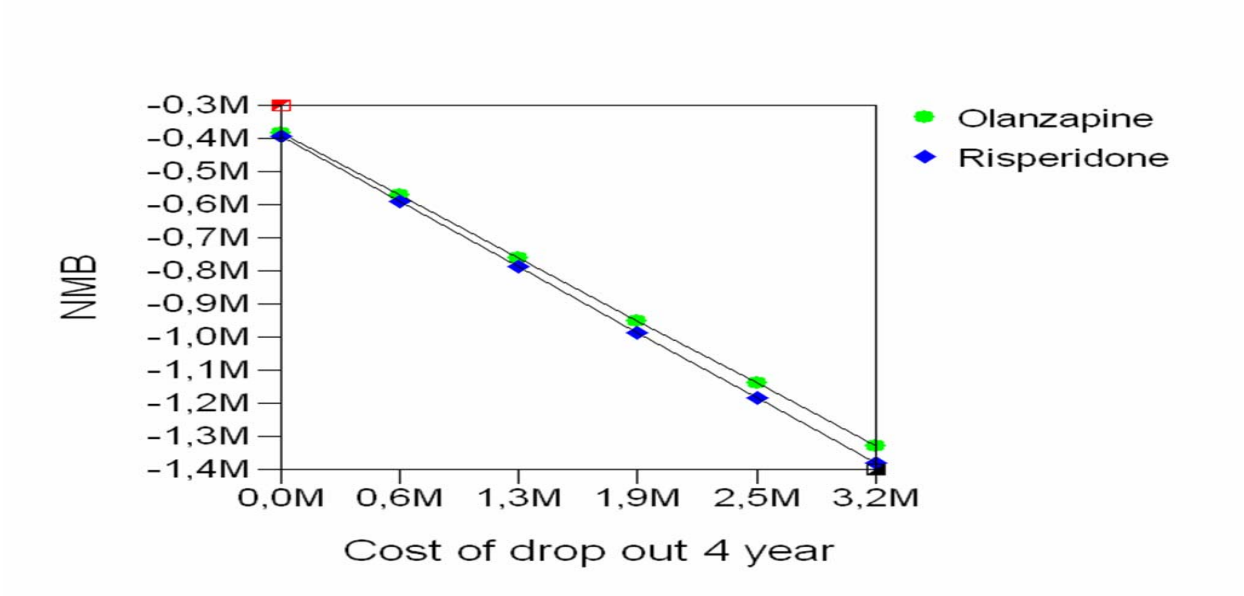
[Appendix VII] A list with all of the probability parameters in the first year in Tornado diagram (NOK in 2008)

Rank	Parameters	Low Input	High Input	Spread
1	probability risperidone drop out	0,1	0,3	9,731,224
2	probability olanzapine drop out	0,1	0,3	9,236,100
3	probability olanzapine adequate respond	0,1	0,3	6,185,932
4	probability olanzapine inadequate respond (less than 20 reduction in PANSS)	0,4	0,6	4,904,604
5	probability risperidone adequate respond(more than 40 reduction in PANSS)	0,1	0,3	4,062,491
6	probability risperidone inadequate respond(less than 20 reduction in PANSS)	0,4	0,6	3,896,226
7	probability olanzapine intolerable adverse events	0	0,2	3,554,748
8	probability risperidone intolerable adverse events	0	0,2	2,476,877
9	probability risperidone suicide attempt	0	0,2	1,787,497
10	probability clozapine suicide attempt	0	0,2	1,444,414
11	probability olanzapine suicide attempt	0	0,2	1,430,651
12	probability clozapine acute relapse	0,6	0,9	102,204
13	probability olanzapine adequate respond noncompliance	0	0,3	72,001
14	probability olanzapine mild respond noncompliance	0	0,3	65,393
15	probability olanzapine adequate respond compliance acute relapse	0	0,2	63,244
16	probability olanzapine mild respond compliance acute relapse	0	0,2	57,440
17	probability risperidone adequate respond compliance acute relapse	0,2	0,4	54,752
18	probability mild respond hospitalization	0,5	0,8	48,812
19	probability clozapine suicide death	0,3	0,5	41,595
20	probability olanzapine suicide death	0,2	0,5	40,851
21	probability risperidone suicide death	0,2	0,4	39,686
22	probability risperidone mild respond compliance acute relapse	0,2	0,4	32,695
23	probability risperidone adequate respond noncompliance	0	0,2	23,790
24	probability olanzapine adequate respond noncompliance acute relapse	0,6	0,9	15,572
25	probability risperidone mild respond noncompliance	0	0,2	14,206
26	probability olanzapine mild respond noncompliance acute relapse	0,6	0,9	14,143
27	probability risperidone acute relapse noncompliance acute relapse	0,6	0,9	10,658
28	probability adequate respond hospitalization	0,5	0,8	9,786
29	probability risperidone mild respond noncompliance acute relapse	0,6	0,9	6,364

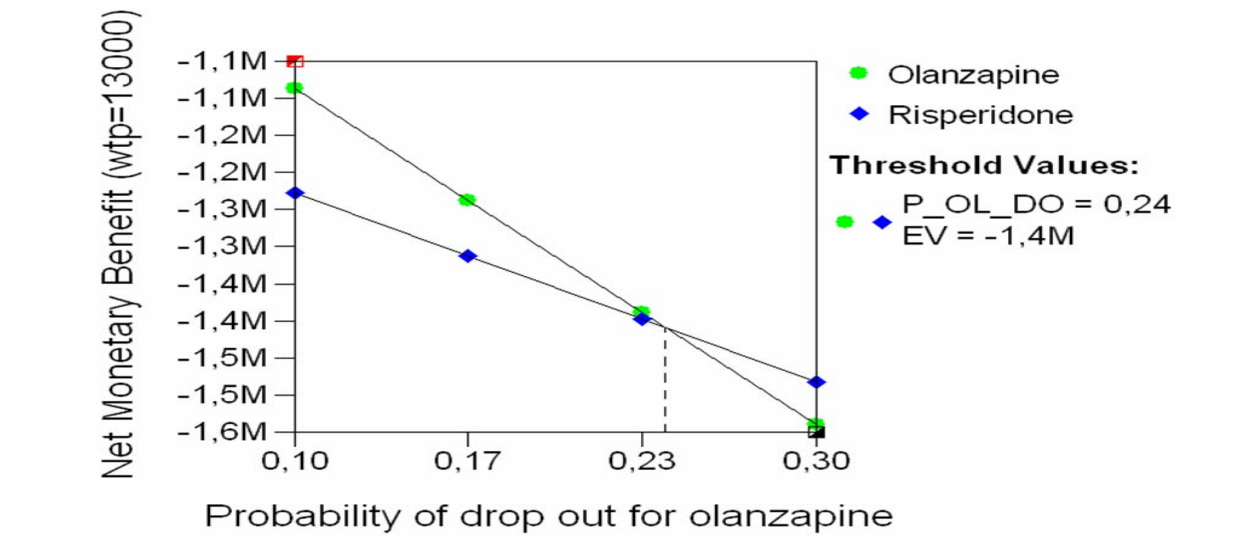
[Appendix VIII] The text report of the Tornado diagram with cost and probability parameters from the second to fifth year, (WTP=13,000)

Rank	Parameters	Low Input	High Input	Spread
1	cost dropout 4year	1500000	3167645	497,764
2	Probability olanzapine drop out	0.1	0.3	393,543
3	probability risperidone drop out	0.1	0.3	324,754
4	probability olanzapine inadequate respond	0.4	0.6	105,190
5	probability clozapine acute relapse	0	0.2	85,077
6	cost mild respond community based care residential care	10402	19319	61,654
7	cost mild respond 2nd line hospitalized care	125377	232844	59,438
8	probability olanzapine intolerable adverse events	0	0.2	49,979
9	probability mild respond hospitalization	0.5	0.8	41,314
10	probability risperidone adequate respond	0.1	0.3	38,763
11	probability risperidone inadequate respond	0.3	0.6	36,811
12	probability olanzapine mild respond noncompliance acute relapse	0	0.2	36,047
13	cost adequate respond CBC residential care	10402	19319	29,112
14	probability risperidone acute relapse noncompliance acute relapse	0	0.2	28,116
15	probability olanzapine adequate respond noncompliance acute relapse	0	0.2	26,203
16	cost mild respond CBC clinical management stable maintenance	4207	7814	23,788
17	probability risperidone mild respond compliance acute relapse	0.2	0.4	21,529
18	probability risperidone suicide attempt	0	0.2	17,253
19	cost mild respond 1st line hospitalized care	74019	137464	12,162
20	cost adequate respond CBC clinical management stable maintenance	4207	7814	11,420
21	cost adequate respond 2nd line hospitalized care	125377	2328441	9,737
22	probability adequate respond hospitalization	0.5	0.8	9,538
23	probability risperidone mild respond noncompliance	0	0.2	9,313
24	cost adequate respond 1st line hospitalized care	74019	137464	8,841
25	probability risperidone intolerable adverse events	0	0.2	8,698
26	probability olanzapine suicide attempt	0	0.2	7,028
27	probability clozapine suicide attempt	0	0.2	6,014
28	cost mild respond drug olanzapine	1742	3742	5,461
29	probability risperidone mild respond noncompliance acute relapse	0.6	0.9	4,170
30	cost mild respond CBC clinical management acute relapse	12320	22880	3,370
31	cost adequate respond risperidone 4mg 3months	364	2364	2,339
32	cost mild respond drug risperidone	364	2364	2,042
33	cost adequate respond olanzapine 10mg 3 month	2742	3742	1,984
34	cost adequate respond CBC clinical management acute relapse	12320	22880	1,040
35	probability risperidone suicide death	0.3	0.5	954
36	probability clozapine suicide death	0.3	0.5	365
37	probability olanzapine suicide death	0.3	0.5	285
38	cost suicide attempt	11123	20658	134
39	cost suicide death	3438	6386	27

[Appendix IX] One-way sensitivity analysis on parameters from the second to fifty year NMB (WTP=13,000)

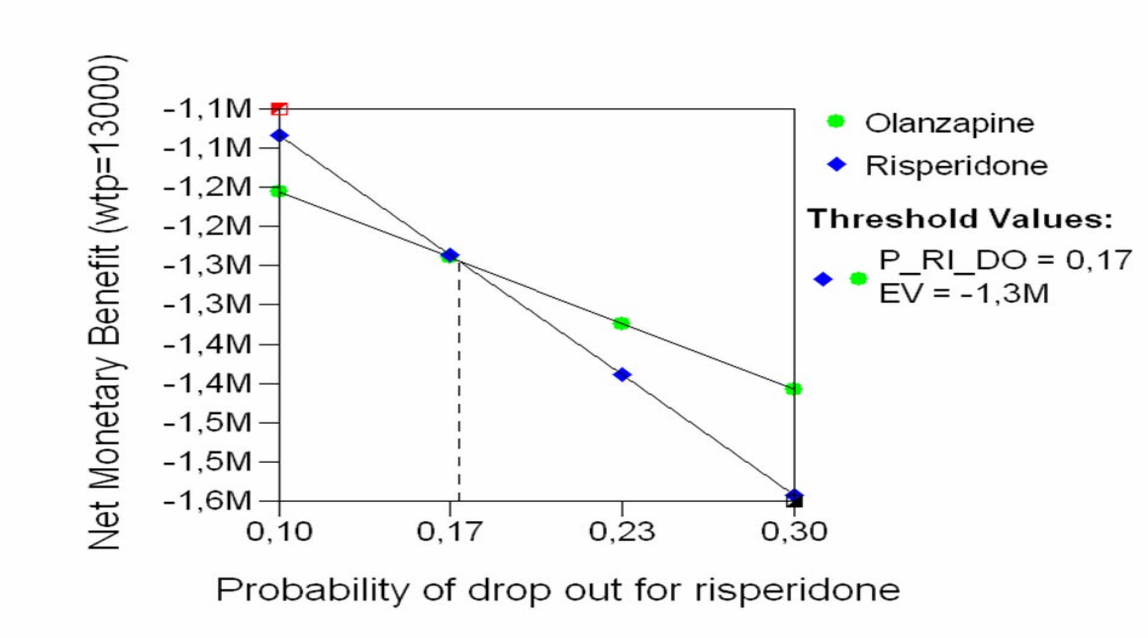


a) One-way sensitivity analysis on the drop out cost for 4 years



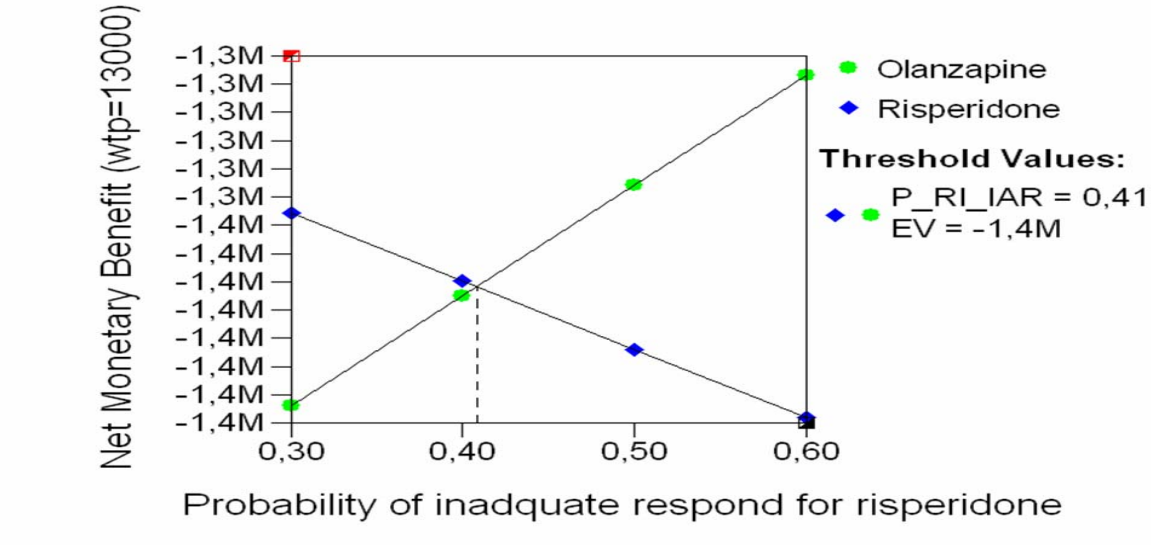
*P_OL_DO: probability of drop out for patients with olanzapine / EV: expected value

b) One-way sensitivity analysis on the probability of drop out for olanzapine



*P_RI_DO: probability of drop out for patients with risperidone / EV: expected value

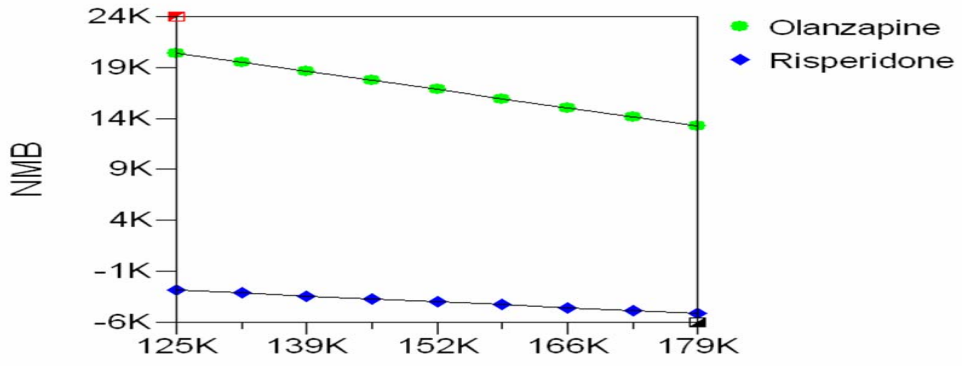
c) One-way sensitivity analysis on the probability of drop out for risperidone



*P_RI_IAR: probability of inadequate respond for patients with risperidone / EV: expected value

d) One-way sensitivity analysis on the probability inadequate respond for risperidone

[Appendix X] Sensitivity Analysis on cost of hospitalized care for the 2nd line respondent with the adequate respond, Net Monetary Benefit (WTP=5,000)



Cost of hospitalized care for the 2nd line respondent with the adequate respond

[Appendix XI] Types of distribution

1. r (=occurrences) and n (=population size) in Beta distribution (integer form)

Beta distribution (integer form)

Formula: $f(x) = \frac{(n-1)!}{(r-1)!(n-r-1)!} x^{r-1}(1-x)^{n-r-1}$

Domain: $0 < x < 1$

Parameters: $r > 0,\ n > r$

Details: Mean = r/n; r = occurences; n = population size

2. α (=alpha) and β (=beta) in Beta distribution (real number form)

Beta distribution (real number form)

Formula: $f(x) = x^{(a-1)}(1-x)^{(b-1)} \frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)}$

Domain: $0 < x < 1$

Parameters: $a > 0,\ b > 0$

Details: Mean = $a/(a+b)$

The parameters a and b can be approximated in TreeAge Pro from mean and standard deviation:

a = mean^2*(1-mean)/(se^2)

b = mean*(1-mean)/(se^2)-a

3. α (=alpha) and λ (=lambda) in Gamma

Formula: $f(x) = \frac{\lambda^{\alpha} x^{\alpha-1}}{\Gamma(\alpha)} e^{-\lambda x}$

Domain: $x > 0$

Parameters: $\alpha > 0,\ \lambda > 0$

Details: Mean = a / λ

The parameters a and λ can be approximated from a mean and standard deviation:

α = (mean^2)/(se^2)

λ = mean/(se^2)

[Appendix XII] The input parameters in the PSA

	The first year					
Index	Description	Parameter. 1	Parameter. 2	Type	Option	Help/Explanation
1	olanzapine drop out	614	116	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
2	Olanzapine continue	614	498	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
3	olanzapine adequate respond	277	50	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
4	olanzapine mild respond	277	69	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
5	olanzapine inadequate respond	277	158	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
6	olanzapine intolerable AE	336	32	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
7	olanzapine tolerable AE	336	304	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
8	olanzapine noncompliance	682	96	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
9	olanzapine compliance	682	586	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
10	olanzapine adequate respond noncompliance acute relapse	0,6	0.9	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
11	olanzapine mild respond noncompliance acute relapse	0,6	0.9	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
12	olanzapine adequate respond compliance acute relapse	1.8113858674	16.6721433918	Beta	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
13	olanzapine mild respond compliance acute relapse	1.8113858674	16.6721433918	Beta	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
14	olanzapine adequate respond acute relapse 2+	0.0752	0.1128	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
15	olanzapine mild respond acute relapse 2+	0.0752	0.1128	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
16	adequate respond hospitalized	3.286	1.769	Beta	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
17	mild respond hospitalized care	3.286	1.769	Beta	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
18	olanzapine suicide attempt	783	10	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
19	risperidone drop out	603	133	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
20	risperidone continue	603	470	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
21	risperidone adequate respond	275	62	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
22	risperidone mild respond	275	55	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
23	risperidone inadequate respond	275	158	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
24	risperidone intolerable AE	341	33	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
25	risperidone	341	308	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer

	tolerable AE					parameters only; 2 = Real-numbered parameters
26	risperidone noncompliance	679	78	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
27	risperidone compliance	679	601	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
28	risperidone adequate respond noncompliance acute relapse	0.6	0.9	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
29	risperidone mild respond noncompliance acute relapse	0.6	0.9	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
30	risperidone adequate respond compliance acute relapse	1.2426153598	2.1618102834	Beta	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
31	risperidone mild respond compliance acute relapse	1.2426153598	2.1618102834	Beta	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
32	risperidone adequate respond acute relapse 2+	0.0752	0.1128	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
33	risperidone mild respond acute relapse 2+	0.0752	0.1128	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
34	clozapine acute relapse	0.6	0.9	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
35	clozapine acute relapse 2+	0.0752	0.1128	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
36	risperidone suicide attempt	777	14	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
37	cost drop out 1st year	4.5000000000	0.0000075766	Gamma	-	Param 1 = alpha; Param 2 = lambda
38	adequate respond hospitalized care 1st	74019.414	137464.626	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
39	adequate respond hospitalized care 2nd	125377.602	232844.118	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
40	cost suicide attempt	11123.763	20658,417	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
41	cost suicide death	3438.799	6386.341	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
42	olanzapine mild respond noncompliance	682	96	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
43	risperidone mild respond noncompliance	679	78	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
44	adequate respond community based care clinic management stable	4207.910	7814.690	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
45	adequate respond community based care clinical management acute relapse	12320.280	22880.520	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
46	adequate respond community based care residential care	10402.686	19319.274	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters

47	mild respond community based care stable	12320.280	22880.520	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
48	mild respond CBC acute relapse	12320.280	22880.520	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
49	mild respond CBC residential care	10402.686	19319.274	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
50	mild respond hospitalized care fist	74019.414	137464.626	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
51	mild respond hospitalized care 2+	125377.602	232844.118	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
52	acute stage hospitalization 1st line cost	51170.700	95031.300	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
53	cost acute stage hospitalization 2nd	102341.400	190062.600	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
54	cost drop out 2+	4.5000000000	0.0000018942	Gamma	-	Param 1 = alpha; Param 2 = lambda

The second to the fifth year

Index	Description	Param. 1	Param. 2	Type	Option	Help/Explanation
1	olanzapine drop out	614	116	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
2	olanzapine continue	614	498	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
3	olanzapine adequate respond	277	50	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
4	olanzapine mild respond	277	69	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
5	olanzapine inadequate respond	277	158	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
6	olanzapine intolerable AE	336	32	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
7	olanzapine tolerable AE	336	304	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
8	olanzapine noncompliance	682	96	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
9	olanzapine compliance	682	586	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
10	olanzapine adequate respond noncompliance acute relapse	0.6	0.9	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
11	olanzapine mild respond noncompliance acute relapse	0.6	0.9	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
12	olanzapine adequate respond compliance acute relapse	1.8113858674	16.6721433918	Beta	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
13	olanzapine mild respond compliance acute relapse	1.8113858674	16.6721433918	Beta	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
14	olanzapine adequate respond acute relapse 2+	0.0752	0.1128	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
15	olanzapine mild respond acute relapse 2+	0.0752	0.1128	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
16	adequate respond hospitalized	3.286	1.769	Beta	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered

						parameters
17	mild respond hospitalized care	3.286	1.769	Beta	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
18	olanzapine suicide attempt	783	10	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
19	risperidone drop out	603	133	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
20	risperidone continue	603	470	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
21	risperidone adequate respond	275	62	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
22	risperidone mild respond	275	55	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
23	risperidone inadequate respond	275	158	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
24	risperidone intolerable AE	341	33	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
25	risperidone tolerable AE	341	308	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
26	risperidone noncompliance	679	78	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
27	risperidone compliance	679	601	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
28	risperidone adequate respond noncompliance acute relapse	0.6	0.9	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
29	risperidone mild respond noncompliance acute relapse	0.6	0.9	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
30	risperidone adequate respond compliance acute relapse	1.2426153598	2.1618102834	Beta	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
31	risperidone mild respond compliance acute relapse	1.2426153598	2.1618102834	Beta	2	Param 1 = alpha; Param 2 = beta. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
32	risperidone adequate respond acute relapse 2+	0.0752	0.1128	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
33	risperidone mild respond acute relapse 2+	0.0752	0.1128	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
34	clozapine acute relapse	0.6	0.9	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
35	clozapine acute relapse 2+	0.0752	0.1128	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
36	risperidone suicide attempt	777	14	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
37	cost drop out 1st year	4.5000000000	0.0000075766	Gamma	-	Param 1 = alpha; Param 2 = lambda
38	adequate respond hospitalized care 1st	74019.414	137464.626	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
39	adequate respond hospitalized care 2nd	125377.602	232844.118	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
40	cost suicide attempt	11123.763	20658.417	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
41	cost suicide death	3438.799	6386.341	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters

42	olanzapine mild respond noncompliance	682	96	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
43	risperidone mild respond noncompliance	679	78	Beta	1	Param 1 = n; Param 2 = r. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
44	adequate respond community based care clinic management stable	4207.910	7814.690	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
45	adequate respond community based care clinical management acute relapse	12320.280	22880.520	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
46	adequate respond community based care residential care	10402.686	19319.274	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
47	mild respond community based care stable	12320.280	22880.520	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
48	mild respond CBC acute relapse	12320.280	22880.520	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
49	mild respond CBC residential care	10402.686	19319.274	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
50	mild respond hospitalized care fist	74019.414	137464.626	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
51	mild respond hospitalized care 2+	125377.602	232844.118	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
52	acute stage hospitalization 1st line cost	51170.700	95031.300	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
53	cost acute stage hospitalization 2nd	102341.400	190062.600	Uniform	2	Param 1 = Low Value; Param 2 = High Value. Option: 1 = Integer parameters only; 2 = Real-numbered parameters
54	cost drop out 2+	4.5000000000	0.0000018942	Gamma	-	Param 1 = alpha; Param 2 = lambda